2015-1588

In the United States Court of Appeals for the Federal Circuit

WARNER CHILCOTT COMPANY, LLC, WARNER CHILCOTT (US), LLC,
Plaintiffs-Appellants,

v.

TEVA PHARMACEUTICALS USA, INC.,
Defendant-Appellee,

RANBAXY, INC., RANBAXY LABORATORIES LIMITED,
WATSON LABORATORIES, INC. – FLORIDA,
Defendants.

Appeal from the United States District Court for the District of New Jersey in Case No. 11-cv-6936, Judge Faith S. Hochberg and Judge Stanley R. Chesler

PRINCIPAL BRIEF OF PLAINTIFFS-APPELLANTS

NONCONFIDENTIAL VERSION

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CERTIFICATE OF INTEREST

Counsel for Warner Chilcott Company, LLC and Warner Chilcott (US), LLC, certify the following:

1. The full name of every party or amicus represented by me is:

Warner Chilcott Company, LLC and Warner Chilcott (US), LLC

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Warner Chilcott Company, LLC and Warner Chilcott (US), LLC

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Warner Chilcott Company, LLC is wholly owned by (i) WC Pharmaceuticals I Limited and (ii) Actavis Puerto Rico Holdings Inc. WC Pharmaceuticals I Limited is wholly owned by Actavis WC 2 S.a.r.l., which is wholly owned by Actavis WC 1 S.a.r.l. Actavis Puerto Rico Holdings Inc. is wholly owned by (w) Actavis Pharma, Inc., (x) Actavis Laboratories UT, Inc. (fka Watson Laboratories, Inc. (Delaware)), (y) Watson Laboratories, Inc. (Corona) and (z) Actavis, Inc. Actavis Pharma, Inc., Watson Laboratories, Inc. (Corona) and Actavis Laboratories UT, Inc. are each wholly owned by Actavis, Inc., which is wholly owned by Actavis W.C. Holding Inc., which is wholly owned by Actavis Capital S.a.r.l., which is owned by (aa) Actavis Ireland Holding Limited and (bb) Actavis WC 2 S.a.r.l., which his wholly owned by Actavis WC 1 S.a.r.l. Actavis Ireland Holding Limited and Actavis WC 1 S.a.r.l. are each wholly owned by Warner Chilcott Holdings Company III, Limited, which is wholly owned by Warner Chilcott Holdings Company II, Limited, which is wholly owned by Warner Chilcott Company Limited which is wholly owned by Warner Chilcott plc, which is wholly owned by Allergan plc (f/k/a Actavis plc).

Warner Chilcott (US) LLC is wholly owned by Warner Chilcott Corporation, which is wholly owned by Actavis W.C. Holding Inc., which is wholly owned by Actavis Capital S.a.r.l., which is owned by (aa) Actavis Ireland Holding Limited and (bb) Actavis WC 2 S.a.r.l., which his wholly owned by Actavis WC 1 S.a.r.l. Actavis Ireland Holding Limited and Actavis WC 1 S.a.r.l. are each wholly owned by Warner Chilcott Holdings Company III, Limited, which is wholly owned by

Warner Chilcott Holdings Company II, Limited, which is wholly owned by Warner Chilcott Company Limited which is wholly owned by Warner Chilcott plc, which is wholly owned by Allergan plc (fka Actavis plc).

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

George F. Pappas; Jeffrey B. Elikan; Kevin B. Collins; Eric Sonnenschein; R. Jason Fowler; Michelle L. Morin; Courtney Forrest; Brianne Bharkhda; Bradley K. Ervin; and Kathryn S. Garcin of Covington & Burling, LLP; Cynthia S. Betz and Jonathan M.H. Short of McCarter English, LLP; Thomas Poché and Amy Hulina of Actavis.

Date: June 26, 2015

Respectfully Submitted:

/s/ Jeffrey B. Elikan
Jeffrey B. Elikan

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STATEMENT OF RELATED CASES

Counsel for Warner Chilcott Company, LLC and Warner Chilcott (US), LLC are not aware of any other cases pending in this or any other court that will directly affect, or be directly affected by, this Court's decision in this appeal.

TABLE OF ABBREVIATIONS

’459 patent	U.S. Patent Number 7,645,459 (DTX-2)
’460 patent	U.S. Patent Number 7,645,460 (DTX-3)
ANDA	Abbreviated New Drug Application
EDTA	disodium ethylene diamine tetraacetic acid
PEA	pharmaceutically effective absorption
Warner Chilcott	Warner Chilcott Company LLC and Warner Chilcott (US), LLC
Teva	Teva Pharmaceuticals USA, Inc.
FDA	U.S. Food and Drug Administration
PTO	U.S. Patent and Trademark Office
POSA	Person of Ordinary Skill in the Art
BR ’601	Brazilian Patent Application No. BR2001-06601 (DTX-205)
Poiger	1978 Poiger reference (DTX-62)
WO ’111	WO 00/61111 patent application (DTX-206)
Mahé	1992 Mahé reference (DTX-209)

STATEMENT REGARDING CONFIDENTIALITY

The non-confidential brief omits certain technical information cited in trial exhibits that the parties designated as Confidential under the protective order issued by the district court in this case. This confidential information includes proprietary information about the parties' product development and manufacturing processes and confidential disclosures to regulatory agencies.

Confidential information has been omitted from pages 3, 11-13, 17-19, 41, 45, 55, 57-59.

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). The district court entered judgment on March 4, 2015, and denied Warner Chilcott's Fed. R. Civ. P. 59(e) motion to alter or amend judgment on April 23, 2015. Warner Chilcott timely appealed on April 23, 2015. This Court has jurisdiction under 28 U.S.C. § 1295(a).

STATEMENT OF THE ISSUES ON APPEAL

1. Did the district court err in finding the claimed invention obvious when (i) it reconstructed the claimed invention through hindsight, picking and choosing discrete elements from the prior art while ignoring other elements; (ii) the two principal prior art references that it found a POSA would have combined to arrive at the claimed invention conflicted with one another, and were inconsistent with other prior art; and (iii) the prior art warned that including one of the claimed elements in a pharmaceutical formulation would increase intestinal permeability, which would have been seen as undesirable?

2. Did the district court err in failing to properly weigh or in dismissing the substantial, unrefuted objective evidence of nonobviousness, including evidence that Teva's scientists were skeptical of the claimed formulation, failed to achieve its results, and ultimately copied the invention?

INTRODUCTION

Until Warner Chilcott introduced Atelvia®, patients had to fast before taking their osteoporosis medication. Patients often did not comply with the fasting requirement, which greatly reduced the effectiveness of their medication. Atelvia solved this longstanding problem. It is the first bisphosphonate used to treat osteoporosis that can be taken with food. Atelvia took compliance "out of the equation" by delivering pharmaceutically effective absorption ("PEA"), *i.e.* similar drug absorption in the fed and fasted states. '459 patent, 4:59-67 (A76).

Atelvia is an embodiment of claim 16 of the '459 patent and claim 20 of the '460 patent. It uses EDTA, a powerful chelating agent[1] that was thought to be "unsuitable" or "inappropriate" for clinical use because of its "damaging effect" on the gastrointestinal tract. Because EDTA is such a powerful chelator, it was known to chelate not only with ions in food travelling through the gastrointestinal tract, but also with ions lying between the cells lining the walls of the gastrointestinal tract, disrupting and widening the tight junctions between these cells, and potentially allowing absorption of bacteria or other things better kept out of the bloodstream. With an active ingredient, such as a bisphosphonate, that is absorbed *between* the cells lining the gastrointestinal tract, this effect would not

[1] Chelating agents bind—or chelate—to certain metal ions called divalent cations, which include magnesium and iron as well as calcium. A472.

have been expected to lead to PEA, but rather absorption of more drug in a fasted state than would be absorbed when taken with food, which provides a separate source of ions with which EDTA can chelate.

Even after the patent applications that led to the '459 and '460 patents had been published and the patents issued, Teva worked hard to find a different path to success. While it recognized that it could obtain FDA approval only by copying the active ingredient and dose used in Atelvia (35 mg risedronate), [redacted], did Teva copy the 100 mg EDTA dose used in the claimed invention, which had been shown to be not only safe and effective, but also to achieve similar absorption of risedronate in the fed and fasted states.

Relying primarily on a Brazilian patent application, BR '601, that (like all the prior art at issue) was considered by the PTO during the course of patent prosecution, the district court found claims 16 and 20 obvious. It did so by

ignoring this Court's repeated admonitions about the dangers of hindsight and using the prior art to selectively reconstruct the claimed invention. This was a legal error, and it permeates the district court's entire decision, from its framing of the obviousness inquiry "in terms of its solution," *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998), to its selective reading of the prior art, and to its failure properly to weigh overwhelming objective evidence of nonobviousness.

The district court's fundamental legal error is tied to clear errors in assessing the factual components of obviousness. The district court employed factual findings that either lacked record support or directly contradicted other findings. By "imbu][ing] one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge," the court fell "victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

The district court's decision should be reversed.

STATEMENT OF THE CASE

Warner Chilcott acquired the rights to the '459 and '460 patents when it purchased the pharmaceutical business of The Proctor & Gamble Company

("P&G") in 2009. A224-25. Those patents issued on January 12, 2010,[2] and protect Atelvia, the only oral bisphosphonate that can be taken with food. *See* A956.

On June 9, 2011, Teva submitted an ANDA to FDA seeking approval of a generic version of Atelvia, which included a Paragraph IV certification that all claims of the '459 and '460 patents are invalid, unenforceable, or not infringed. A225. On November 22, 2011, Warner Chilcott filed suit against Teva for infringement of the '459 and '460 patents, A163-222, and Teva asserted counterclaims of invalidity. A225.[3] For purposes of the litigation, Teva stipulated to infringement of claim 16 of the '459 patent and claim 20 of the '460 patent. A230. A five-day bench trial on Teva's invalidity counterclaims commenced before the Honorable Faith Hochberg on July 14, 2014.

On March 4, 2015, the district court issued a judgment and opinion finding the asserted claims obvious, but not anticipated. A25, 68; A70-71. On March 20, 2015, Warner Chilcott filed a Fed. R. Civ. P. 59(e) motion to alter or amend judgment, or, in the alternative, for a new trial, to correct the district court's fundamental legal and factual errors in finding the asserted claims obvious. A289-

[2] The applications were published on November 24, 2005 and May 25, 2006.

[3] Warner Chilcott filed suit against additional generic defendants, but those defendants settled prior to trial.

330; A336-57. The district court—now through the Honorable Stanley Chesler, to whom the case was reassigned following Judge Hochberg's retirement—denied Warner Chilcott's Rule 59(e) motion on April 23, 2015, A358-64, and Warner Chilcott timely appealed, A365-66.

STATEMENT OF THE FACTS

A. Osteoporosis and Oral Treatment with Bisphosphonates.

In a healthy individual, bone is continually broken down and replaced in equal amounts by cells known as osteoclasts and osteoblasts. A236; A470. In an individual with osteoporosis, the osteoclast removes more bone than an osteoblast can replenish. A471. Over time, this deficit leaves "the bone…thin and brittle and the patients are prone to fractures." A471.

Bisphosphonates are a class of drugs "prescribed for the treatment of osteoporosis," A3769, and chelate to the calcium on the surface of bone, A471. Bisphosphonate attachment inhibits an osteoclast's ability to remove bone, and allows the osteoblast to replenish more bone than was removed, thereby increasing bone mass over time. A471. As of 2005, the FDA had approved three bisphosphonates—alendronate sodium (Fosamax®), risedronate sodium (Actonel®)[4], and ibandronate sodium (Boniva®)—for the treatment of

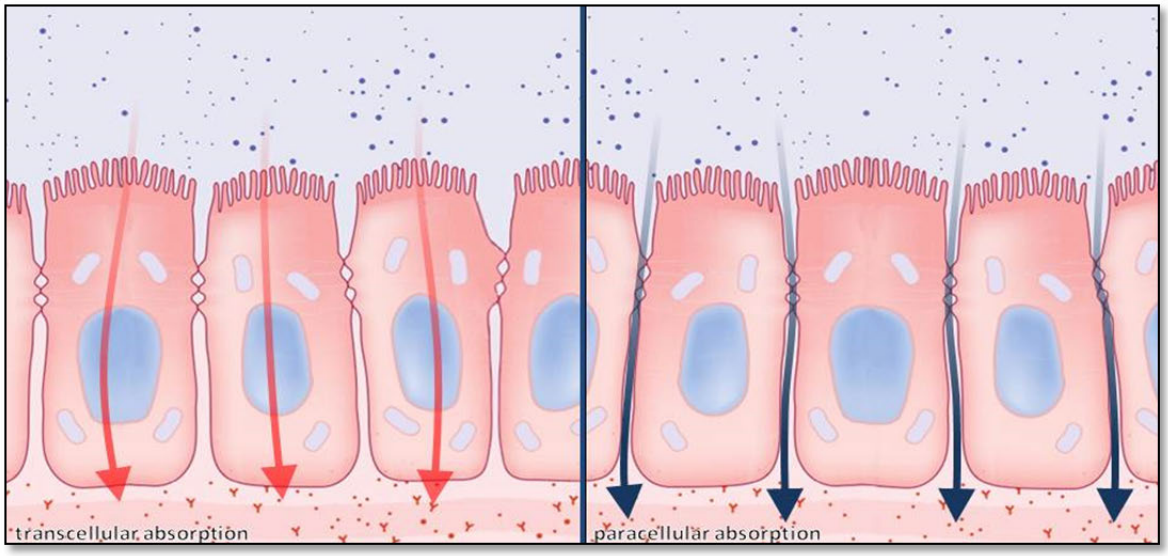
[4] Actonel is owned by Warner Chilcott.

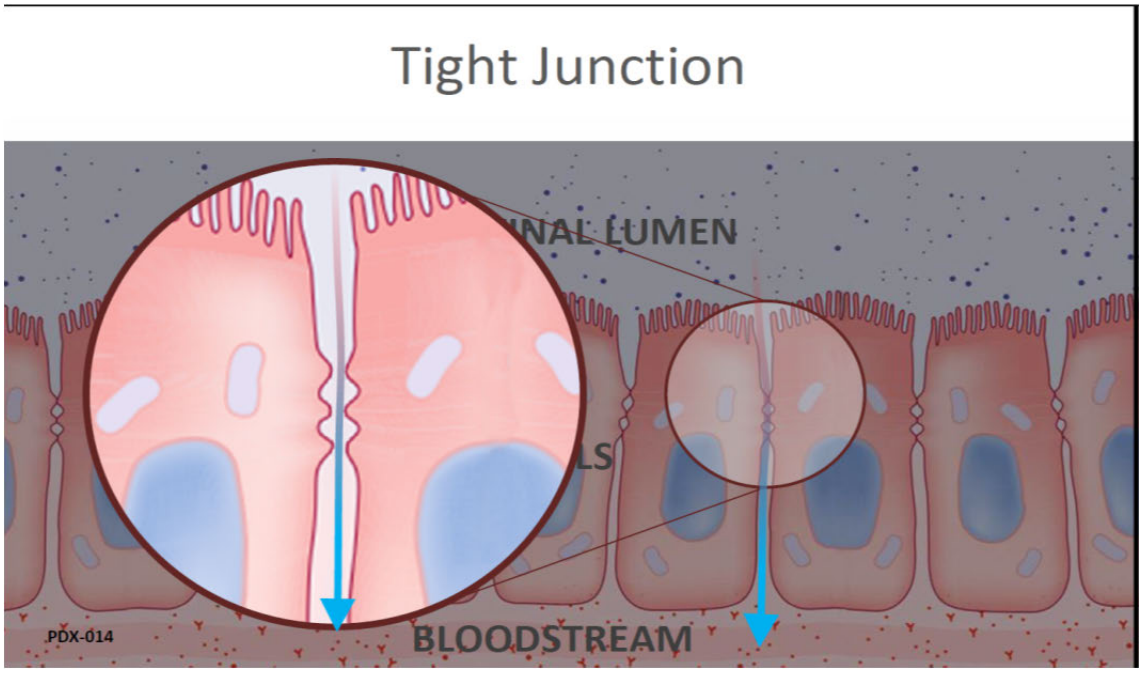
postmenopausal osteoporosis through various oral formulation doses delivered daily, weekly, or monthly. A231-33; A468.

1. Bisphosphonate Absorption and the Food Effect.

Orally administered drugs, like the approved bisphosphonates, enter the patient's gastrointestinal tract for absorption into the bloodstream and ultimate delivery to the drug's site of action. After the stomach, the lower gastrointestinal tract includes the small intestine—which is divided into segments—and the large intestine. A236. As a drug moves through an individual patient's gastrointestinal tract, it encounters variable quantities of food. A706-07; A578-79.

Once in the gastrointestinal tract, a drug can enter the bloodstream in two ways: (1) transcellularly through the cells of the gastrointestinal tract's walls, or (2) paracellularly through the small spaces, called "tight junctions," between the cells of the gastrointestinal tract's walls. A3751-52; A474.





"The tight junctions…are formed by specific protein and divalent cations, such as [calcium and magnesium]." A3752. The tight junctions are gatekeepers that "regulate the passage" of material into the bloodstream, A474, and keep out, among other things, intestinal bacteria and other drugs, A3772. Bisphosphonates are absorbed paracellularly through the tight junctions. A3751; A474.

Because they are absorbed only paracellularly, bisphosphonates have low bioavailability, with less than 1% of the oral dose absorbed. A3733; A3750-51. When taken with food, absorption approaches 0%, "especially in the presence of calcium and iron." A3751. This further dramatic reduction in bioavailability is known as the "food effect" and "is thought to result, at least in part, from…[chelation between the bisphosphonate and] calcium" in the gastrointestinal tract. A3733.

To offset the food effect, the labels of every FDA-approved bisphosphonate prior to Atelvia instructed that the drug be taken in a fasted state "at least one-half hour before the first food, beverage, or medication of the day." A231-32 (Fosamax); *see also* A232 (Actonel); A233 (Boniva) (directing administration "at least 60 minutes before" food, drink or medication). These fasting directions introduce a high compliance burden to osteoporosis treatment: for the drug to be effective patients must not only take the drug *when* directed (daily, weekly, monthly), but also *as* directed (*i.e.*, in a fasted state). A929.

In a 1998 study "more than half" of patients taking a bisphosphonate admitted that they failed to comply with the fasting requirements. A933-34. *See* A3746. Both patients and their doctors may be confused about "how to fit [the patient's] weekly bisphosphonate treatment dosing rules into their daily schedule." A952-53. This is particularly true for patients—such as those commonly undergoing osteoporosis treatment—taking multiple medicines, some of the most common of which often have conflicting dosing instructions (*e.g.*, requiring administration *with* food) to bisphosphonates. *See*, *e.g.*, A3775-76, 79-80. Absent compliance with the fasting requirements, "the absorption of bisphosphonates is obliterated and the drugs simply don't work." A939-40.

2. Proposed Solutions and Safety Concerns with EDTA.

For decades, researchers struggled to address the problems posed by the fasting requirement, including introducing weekly or monthly formulations intended to lower the compliance burden. *See* A476-77. A small handful of researchers sought to overcome the poor bioavailability of bisphosphonates directly, including by administering them in combination with a variety of absorption "enhancers," including chelators like EDTA. *See, e.g.*, A1638-41.

EDTA binds with calcium and metal ions—in food or otherwise—better than bisphosphonates. A3769, 3772; A1137; A3741. Because EDTA is a strong chelator, however, "EDTA can deplete the extracellular [calcium], which is necessary for the maintenance of the" tight junctions that prevent bacteria and other antigens from entering the bloodstream. A3769. *See also e.g.*, A3741 ("As the tight junctions are formed by…divalent cations, …the chelating agents might alter the integrity of the intercelullar tight junctions…."); A3734 ("The mechanism might involve…a change in mucosal permeability."); A3752 ("EDTA complexes the[] cations and widens the paracellular tight junctions…."); A3716 (same).

As a result, researchers cautioned against using EDTA in the decades preceding the claimed invention:

- "[d]espite the strong absorption enhancing properties of EDTA, the applicability of this agent in human pharmacotherapy is *questionable*,

considering its damaging effects on mucosal integrity." A3716-17 (1989) (survey describing prior studies) (emphasis added);

- EDTA is "*unsuitable* for clinical use." A3736 (1990) (emphasis added);
- "[c]oadministration of [a bisphosphonate] with EDTA improves the absorption; however, the clinical use of EDTA is *limited*." A3741 (1994) (emphasis added);
- "this chelator [is] *unsuitable* for clinical use." A3758 (2000) (survey citing prior studies) (emphasis added);
- "the implementation of…EDTA in any kind of clinical study on humans would be *inappropriate*." A3772 (2005) (emphasis added).

See also A4015 (noting FDA's "[redacted]"). The danger posed by EDTA, moreover, would be compounded when EDTA is given in a fasted state because there would be no food in transit through the gastrointestinal tract and, thus, the only source of metal ions would be in the tight junctions. A705-06.

B. The Invention.

1. P&G's Hypothesis and Discovery.

In this environment, P&G scientists Dr. David Burgio and Dr. Richard Dansereau (collectively, "the inventors") set out in early 2000 to "develop a

technology that avoided the food effect while minimizing any exposure when the product was given fasted," A1225, aiming for a product "with no food restrictions." A3861. [redacted] A3861. To solve the problem, the inventors considered (1) the dose of risedronate; (2) the type and dose of chelator to administer with risedronate; and (3) how and where to deliver the formulation in the gastrointestinal tract. A1129-30.

The inventors chose EDTA from a variety of possible chelators, *see* A3865-66; A1136, due to its solubility and its ability to "bind[] about twice as well to calcium" in comparison to risedronate. A1137. But while the inventors "wanted to enable [the absorption of risedronate] in the presence of food," they "did not want to increase the permeation" and damage the integrity of the intestinal tight junctions. A1136-37. What the inventors wanted was PEA: similar absorption in the presence or absence of food. Aware of the prior art cautioning against the clinical use of EDTA, *see* A1138-39, the inventors hypothesized overcoming the danger by "go[ing] with a lower dose [of EDTA] and push[ing] the actual delivery…[to] the ascending colon," rather than the stomach or small intestine where calcium levels are higher and a higher corresponding dose of EDTA would be needed. A1139-40.

At the time, there was "no data [on] bisphosphonate" absorption in "the ascending colon…." A1140-41. An initial nonclinical study on beagles in 2001

returned disappointing results, with absorption of risedronate in the ascending colon "only about five to 10 percent" of the absorption from an immediate-release formulation. A1141-42; *see also* A3874. After these results, P&G's development partner—[redacted]—abandoned the project, A1142, and the inventors needed "about six months to convince…[P&G] to fund" a follow-up study in humans, A1141-42.

In 2003, P&G conducted that first clinical study in the human ascending colon. A1144; A1371-1576. The investigators administered a 50 mg dose of risedronate with a 100 mg dose of EDTA released in the ascending colon in the fasted state. A1147-48; A1371-1576. The test was carried out "in a very controlled environment" in which the subjects—consisting of "healthier people" aged 18 to 45—were "housed…[at the testing facility] for a couple of days" to allow the investigators to "monitor how they're doing." A1145-46, 1148. This first human trial demonstrated risedronate absorption in the colon "just as good or better than the absorption with the immediate release tablet"—the control group for assessing effectiveness. A1148.

P&G conducted a second human study in 2004, which tested risedronate absorption when administered with 100 mg of EDTA in the ascending colon in the fed state. A1149; A3956-57. The study undermined the inventors' hypothesis of delivering the risedronate to the ascending colon, which fell far short of the control

group, A1150-51; A3983. But the study results offered a surprise. Contrary to earlier research indicating that larger doses of EDTA are necessary to increase bisphosphonate absorption "further up the GI tract into the stomach and [small intestine]," A1151; *see also supra* pp. 10-11, the inventors found absorption of risedronate in the small intestine that was similar in the fed and fasted states, and also similar to the control immediate-release risedronate. A1151; A3983.

Further studies confirmed this unexpected result in the small intestine with a formulation containing 35 mg of risedronate and 100 mg of EDTA. A1152-54; A4060.

2. The Patents-in-Suit.

Having met their "high risk" goal, the inventors filed patent applications to protect their invention on April 15, 2005 and November 23, 2005. A230. The Examiner initially rejected the proposed claims as obvious, principally reasoning that a 1994 study by Lin, A3737-42, "teaches [that] EDTA increases the absorption of alendronate…, which is a bisphosphonate drug." A2311; A3502. In response, P&G amended the claims to require PEA. A2812; A3615; A1167-68.

In an examiner interview, Dr. Burgio distinguished Lin, which—like the other investigations of using EDTA—focused on using EDTA to increase permeability, not to achieve PEA. A1167-68. PEA is defined as "an amount of a chelating compound high enough to significantly bind metal ions and minerals in

food but low enough not to significantly alter absorption in the fasted state. That is, absorption is similar with our without food." '459 patent, 4:59-67 (A76).[5] The Examiner was persuaded, and, with the addition of PEA, the '459 and '460 patents issued on January 12, 2010. '459 patent (A75); '460 patent (A103).[6]

Claim 16 of the '459 patent and claim 20 of the '460 patent each consist of an independent claim and several dependent claims. Independent claim 8 provides as follows:

> An oral dosage form having pharmaceutically effective absorption comprising:
>
> (a) from about 1 mg to about 500 mg of risedronate sodium;
>
> (b) from about 75 mg to about 250 mg of disodium EDTA; and
>
> (c) an enteric coating which provides for release of the risedronate sodium and the disodium EDTA in the lower gastrointestinal tract of a mammal.

'459 patent, 38:50-57 (A93). Dependent claim 16, which further depends on dependent claims 13 through 15, provides a specific formulation with PEA, 35 mg of risedronate sodium, 100 mg of EDTA, and an enteric coating that is a methacrylic acid copolymer. '459 patent, 39:5-13 (A94). The '460 patent further

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[5] The '460 specification is substantially similar to the '459 patent.

[6] The PTO considered, among other references, the BR '601 and WO '111 patent applications as well as studies by Lin, Ezra, Mitchell, Janner, Muranishi, Poiger, Whittaker, Mahé, and Zakelj. *See* '459 patent (A72-99).

recites that the enteric coating provide for "immediate release" in the "small intestine." *See* '460 patent, 24:47-55, 25:8-20 (A114-15).

3. FDA Approval of Atelvia.

FDA approved Atelvia, administered once weekly for the treatment of postmenopausal osteoporosis, on October 8, 2010. A234.[7] In contrast to all then-approved oral bisphosphonate formulations, Atelvia's prescribing information states that "Atelvia should be taken in the morning immediately following breakfast." A234-35.[8]

A clinical study leading to FDA approval demonstrated that Atelvia "can be given with clinical effectiveness after breakfast," A912, producing results "similar to or greater than" the existing, approved daily risedronate product (Actonel). A1611.[9] In other words, "the whole aim of the invention was satisfied," A912,

[7] Risedronate sodium is Atelvia's sole active ingredient. EDTA is listed as an inactive ingredient (or excipient).

[8] In other countries, the Atelvia formulation has been approved for administration in both the fed and fasted state. In a clinical study leading to approval, the patients taking the drug in a fasted state had "a higher numeric frequency of upper abdominal pain…." A912-13.

[9] To the "surprise" of the investigators, the study showed a "significantly greater" response in bone density after two years of administration of the claimed formulation in comparison to daily Actonel. A918. Based upon past studies, the investigators reasoned that poor patient compliance with the fasting instructions required by daily Actonel accounted for the better result. A920-30.

eliminating the patient compliance problems that stemmed from bisphosphonate fasting directions. *See supra* p. 9.

Atelvia "didn't just solve the issue about compliance with the dosing rules, it made those rules not be even an issue anymore." A956; A1619 (Atelvia "is more convenient for many subjects with busy schedules or in older subjects who must take many other medications" and avoids "poor compliance with dosing" that "blunt[s] the therapeutic effectiveness of risedronate"). Thus, in comparison to prior bisphosphonate treatments, "[t]he magic of Atelvia is that the dosing rules don't matter…." A929. *See also* A1615 ("None of the current oral bisphosphonate dosing schemes solves the possible detrimental effect of poor compliance with dosing instructions on…clinical effectiveness.").

C. Teva's Failed Attempts to Duplicate the Invention.

Teva sought (and failed) to duplicate Atelvia's magic. Based upon a review of the '459 and '460 patent materials, Teva suspected that "[redacted]." A3786.[10] Teva scientists involved in the development of Teva's product searched

[10] The FDA's Inactive Ingredient Guide ("IIG") "tell[s] manufacturers acceptable amounts of different excipients that can be used in drugs" and "lists amounts based on prior history of the use of the excipient…." A719. At the time, (continued…)

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for scientific support for [redacted], to no avail. *See* A3786 (describing publication search "[redacted]"). [redacted] *See also* A1018-19; A740-41, 744-45. [redacted] A1040, 52, 54-55.[12]

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the IIG listed 5 mg as the maximum approved amount of EDTA. A719; A720. The claimed invention contains 20 times this amount.

[11] These employees included (1) Dr. Cheung, a manager of bioequivalent studies, A745; A1028-32, (2) Dr. Shaik, Teva's Associate Director of Formulation R&D, A1040, 1043-44, and (3) Keith Earle, an internal toxicologist, A1046; A1027.

[12] Teva also experimented with chelators other than EDTA. A1043-44.

CONFIDENTIAL INFORMATION OMITTED

[redacted] A3785. Teva did not conduct studies with a 100 mg EDTA dose until after Atelvia's market launch in 2011. A1050-51. After that, Teva produced a generic product that matched both the type (EDTA) and amount (100 mg) of Atelvia's chelator exactly. The Atelvia formulation remains the only oral bisphosphonate that can be taken with food. A956.

D. Trial Proceedings.

After Warner Chilcott filed suit in response to Teva's ANDA, A225, the case proceeded to a five-day bench trial on Teva's invalidity counterclaims, A225, 230. The trial began with the complete direct, cross, and redirect examinations of Teva's primary witness, Dr. Yates. *See* A369; A506. The district court then asked the parties to make their experts available for "hot-tubbing"—a witness debate format in which the witnesses "have a conversation amongst themselves" subject to questions from the district court and counsel. A694-95. Under this format, Dr. Yates testified on three of the four days that evidence was introduced at trial, and the district court allowed Dr. Yates to testify for a second time on the parties' principal prior art references, A1278-81, A1283-85 (discussing Janner and BR '601), closing out the trial as he had begun it.

1. Teva's Invalidity Case Focused on BR '601 and Poiger.

Teva briefly raised a number of prior art references—nearly all of which the PTO considered prior to issuance, *see supra* n.6—but it focused its invalidity arguments on two references.

BR '601. Teva principally relied upon BR '601, a Brazilian patent application published in September 2003. A1621-33. *See also* A265-67. BR '601 teaches a controlled release formulation for delivering a combination of a bisphosphonate and a chelating agent to the small intestine for the treatment of various diseases, including osteoporosis. A1622-23. It broadly discloses a formulation that consists of any bisphosphonate with a pharmacological effect (reciting 12 specific examples, including risedronate), a chelating agent (four examples are provided, one of which is EDTA in its salt or acid forms), and any polymer that can form a film soluble in the gastric pH (multiple examples, one of which is methacrylic acid copolymer). BR '601 explains how its formulations operate: (1) by providing the chelating agent to the small intestine rather than the stomach, (2) chelating to ions in the small intestine in preference to the bisphosphonate, allowing the latter to be absorbed, and (3) "increas[ing] the permeability of the intestinal mucosa, thereby increasing the capacity to absorb bisphosphonate." A1624-25.

As to the dose of the bisphosphonate, it states that "an effective quantity…for example between 1 and 150 mg" should be administered "at regular intervals (for example, daily or weekly) or irregular intervals with immediate, delayed, and prolonged release of the bisphosphonate, with a time interval, effective quantity, and rate of release depending on the disease to be treated and as known to a person skilled in the art." A1628. It then states the signal achievement of the invention: "we obtain an effective treatment with a small quantity of bisphosphonate as compared to the current treatment by its association with a chelating agent…." A1625; *see also* A1623 (low oral bioavailability of bisphosphonates "necessitates the use of high doses of the drug in relation to the quantity actually absorbed by the body" with undesirable consequences).

As to the dose of chelating agent, BR '601 provides that it may be determined proportionally by reference to the bisphosphonate dose selected: "[a]ccording to a particular embodiment of the invention, the proportion between the quantities of chelating agent and bisphosphonate is greater than 10% mol/mol, particularly higher than 50% mol/mol." A1627. It also states that "[i]t is preferable but not exclusively preferable for the daily intake of chelating agent, particularly EDTA, not to exceed 175 mg." A1627.

Dr. Yates testified that "BR 601 discloses every element" of the claimed delayed release formulation, including the bisphosphonate dose (reading the term

"effective quantity" to point to the conventional 35 mg dose used in immediate release Actonel) and the EDTA dose (the approximate midpoint in the proportionally derived 20-175 mg range). *See* A488. A489-90, 492-95; A1623, 26, 27; A232 (describing Actonel). Dr. Yates even divined PEA from BR '601 by equating its supposed goal of "overcoming the food effect" with "achieving pharmaceutically effective absorption." A500. As a fallback, Teva also alleged obviousness based on BR '601, to which it proposed additional references to overcome BR '601's shortcomings. Principal among these references was Poiger.

Poiger. Poiger, published in 1976—years before BR '601 and the numerous references warning against using EDTA—describes a study of 500 mg tetracycline, another poorly absorbed drug, in five fasting patients when administered with (1) water alone, (2) 500 mg EDTA and water, (3) 200 ml milk, and (4) 200 ml milk, water, and a 2.3 gram solution of EDTA. *See* A1608-09. To avoid side effects, the authors used a different form of EDTA—tetrasodium EDTA—or sodium hydroxide to "neutraliz[e]" the administered EDTA dose. A1609-10.[13] The results of this small study was that absorption of tetracycline was unaffected by EDTA, and that EDTA appeared to counteract the food effect exercised by the

[13] Specifically, (a) in Experiment 2, Poiger administered 250 mg of disodium EDTA and 250 mg of tetrasodium EDTA; and (b) in Experiment 4, Poiger dissolved 2.3 grams of disodium EDTA in water and adjusted the pH level with sodium hydroxide. A1608.

milk when administered in an amount "equivalent as a molar ratio to the amount of calcium present" in the milk. A1609. Poiger noted that the conclusion that absorption of tetracycline was unaffected by EDTA was contrary to the results obtained in two other studies, and attempted to explain the different results, in part, by its use of tetrasodium EDTA instead of the (claimed) disodium EDTA used in the other studies. A1609-10.

Dr. Yates testified that Poiger showed that (1) EDTA reversed the "suppression of tetracycline absorption" by the milk, A516, and (2) when administered with EDTA, "the bioavailability of the drug remained constant irrespective of the diet[,]…a description of [PEA]." A517-18. He also testified that Poiger demonstrates EDTA safety. A519. Yet Dr. Yates acknowledged that Poiger exactly matched the amount of EDTA administered with the amount of milk, A516, even though, as he conceded, a POSA could not know in advance the amount of food that a given EDTA dose would encounter in any given area of a patient's small intestine. A572, 576-79. Dr. Yates further conceded that Poiger altered the EDTA to avoid its known safety issues. A584-85.[14] Dr. Yates did not explain why different results were obtained in the two other studies referenced in

[14] To support its argument that a skilled artisan would understand that EDTA is safe for human use, Teva also relied on literature relating to EDTA's use as a food additive. A672-94. Teva's expert, however, conceded that a food additive is "swallowed with food," A686, to which the EDTA may chelate before reaching the intestinal tight junctions.

Poiger, A514-19, or why he believed the results obtained in Poiger's five-person study were more reliable than those obtained in the other studies. A583-84.

2. Decision on Appeal.

On March 4, 2015, the district court entered judgment holding claim 16 of the '459 patent and claim 20 of the '460 patent invalid as obvious. A68; A70-71. The court further held, however, that Teva failed to prove by clear and convincing evidence that BR '601 anticipates the asserted claims. A25; A70. The district court's decision rests on a handful of key findings.

First, the district court found that the physical ingredients of the claimed invention—risedronate, EDTA, and the enteric coating—are included among BR '601's laundry list of bisphosphonates, chelating agents, and delivery agents. A14-15. The district court also determined that BR '601 disclosed dose ranges encompassing those used in the claimed invention—an "effective" dose of a bisphosphonate, which would include the 35 mg risedronate dose used in Actonel; and an EDTA dose range (proportional to the 35 mg risedronate dose) of between 20 and 175 mg. A15-16. Although BR '601 did not point specifically to 100 mg EDTA, the district court found that dose was not "critical" to the invention because (1) the claimed risedronate and EDTA doses "work independently of each other," and (2) the '459 and '460 specifications include ranges and examples of formulations covering a wide variety of doses. A18-19. Thus, in the district

court's view, BR '601's ranges of listed ingredients rendered obvious the claimed formulation. A50-51.[15] The district court (correctly) concluded, however, that BR '601 does not disclose PEA. A25.

Searching for a prior art source of PEA, the district court turned to Poiger. *See* A30-32, 57-61. According to the district court, Poiger "would have motivated a person of skill in the art to modify [BR '601] to include" PEA due to Poiger's "success achieving 'almost equivalent' absorption 'irrespective of the diet' using EDTA as a chelator of calcium." A57. Indeed, the district court believed that Poiger would motivate a skilled artisan to "use EDTA solely as a chelator to bind calcium from food," A57-58, and not to "enhance intestinal permeability," A56. The district court found Poiger to be "powerful evidence for a skilled artisan," A61, to disregard BR '601's teaching that increased intestinal permeability begins with 20 mg of EDTA, and instead insert the district court's reading of Poiger into BR '601 to achieve PEA, A57-58.[16]

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[15] The district court further concluded that a person of ordinary skill would not have been deterred from clinical use of a 100 mg EDTA dose based on, principally, BR '601's disclosure of an EDTA range up to 175 mg, A32, the Poiger study's use of a 250 mg EDTA dose, A39, 53, and statements made by P&G to obtain FDA approval of its clinical trials, A39-40.

[16] The district court also pointed to WO '111 as "suggest[ing] using a chelating agent to achieve similar absorption of bisphosphonates regardless of food intake." A56-57.

Against this evidence, the district court failed properly to weigh or else dismissed the majority of Warner Chilcott's objective evidence of nonobviousness, including Teva's skepticism, failed attempts to achieve the invention, and ultimate copying of the claimed invention. A66-67. Instead, the district court gave weight to Teva's evidence that a P&G sub-licensee (Takeda) simultaneously claimed an invention "minimizing absorption variation due to interaction with food," using citric acid as a chelator. A46; A1577-1604. The district court also weighed Warner Chilcott's evidence that Atelvia satisfies "some" need for "an osteoporosis drug that lessened the consequence of failure to fast," but found it "not sufficient to outweigh the extensive evidence in the prior art showing that coadministration of EDTA and a bisphosphonate would have the benefit of reducing the food effect." A66-67.

SUMMARY OF THE ARGUMENT

Under a well-established principle of patent law, it is "impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (quotation omitted). By engaging in hindsight reconstruction of the prior art from the perspective of the claimed invention, the district court committed a reversible error of law.

1. The district court fell "victim to the insidious effect" of hindsight. *W.L. Gore*, 721 F.2d at 1553. The court's error infected every stage of its analysis, and is evident in repeated and significant erroneous factual findings made without record support or in direct contradiction of other factual findings made by the district court.

The district court relied on hindsight knowledge of the invention's success to (a) frame the obviousness inquiry in terms of the claimed solution in the invention; (b) fundamentally misunderstand, contrary even to the prior art references on which it relied, the nature of EDTA's mechanism of action; (c) pick and choose isolated disclosures from the prior art, and, in the process, disregard overwhelming evidence that the prior art taught away from using EDTA in the claimed invention; and (d) selectively ignore the conflicting teachings of its primary references—BR '601 and Poiger—to generate a motivation to achieve the claimed invention through their combination that lacks any legally sufficient support in expert testimony.

2. The district court did not appropriately weigh all "objective indicia [to] guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012) (quotation omitted). The district court dismissed Warner Chilcott's overwhelming evidence, which Teva did not

adequately rebut, that Teva itself (a) tried and failed to achieve the claimed invention; (b) expressed skepticism that the claimed invention could include a 100 mg dose of EDTA given the long-standing warnings against clinical use of EDTA; and (c) copied the claimed invention after Atelvia's market launch. In dismissing this evidence, the district court again relied upon unsupported and internally inconsistent factual findings to construct a selective view of the record.

ARGUMENT

Under 35 U.S.C. § 103(a), obviousness involves interrelated legal and factual inquiries. In the standard formulation, "[o]bviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012). As the party asserting obviousness, Teva bears "the burden to show by clear and convincing evidence" that the asserted claims would have been obvious to a POSA at the time of the invention. *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1293-94 (Fed. Cir. 2013).

Although Teva convinced the district court that it carried this hefty burden, the record is to the contrary. "Following a bench trial, [this Court] review[s] the district court's conclusions of law *de novo* and its findings of fact for clear error."

Otsuka Pharm. Co., Ltd. v. Sandoz, Inc., 678 F.3d 1280, 1290 (Fed. Cir. 2012). The district court's judgment falls short on both the law and the facts. Two fundamental legal errors underlie the district court's analysis: (1) use of improper hindsight reasoning to reconstruct the claimed invention from selected portions of the prior art, and (2) dismissal of unrefuted objective evidence of nonobviousness. The district court also made a series of clearly unsupported or internally inconsistent factual findings.

I. The District Court Erred as a Matter of Law by Using Hindsight Reasoning.

In assessing obviousness, the question is "*not* what would be obvious to a judge after reading the patents in suit and hearing the testimony." *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1092 (Fed. Cir. 1985). To the contrary, "[t]hat which may be made clear and thus obvious to a court, with the invention fully diagrammed and aided by experts in the field, may have been a breakthrough of substantial dimension when first unveiled." *Mintz*, 679 F.3d at 1378 (quotation omitted). Indeed, "[i]nventions in most instances rely upon building blocks long since uncovered, and combine elements that are in some sense already known." *Ortho-McNeil Pharm., Inc. v. Teva Pharm. Indus., Ltd.*, 344 F. App'x 595, 598 (Fed. Cir. 2009).

As a result, a reviewing court must guard against hindsight reconstruction of the prior art from the perspective of the achieved invention. "The inventor's own

path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Otsuka Pharm.*, 678 F.3d at 1296. A district court commits legal error when it uses hindsight as a lens to find obviousness. *See Mintz*, 679 F.3d at 1377 ("reliance on hindsight" is "prohibited"); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (guarding against "non-statutory hindsight analysis"). Here, hindsight infected every phase of the district court's analysis and "provides the only discernable reason," *Kinetic Concepts*, 688 F.3d at 1360, to construct the claimed invention from the prior art in this case.

For decades, researchers investigated the impact of EDTA on bisphosphonate absorption, consistently warning against clinical use of EDTA in light of its ability to damage the tight junctions. *See supra* pp. 10-11. The district court's primary reference, BR '601, aimed at decreasing the effective bisphosphonate dose by ***increasing*** intestinal permeability through EDTA doses that are "preferably, but not exclusively preferably" as low (assuming 35 mg of risedronate is used as the bisphosphonate) as 20 mg. *See supra* pp. 20-22. The inventors chose a different route, achieving PEA—similar absorption in the fed and fasted states—to specifically avoid "increas[ing] the permeation" and damaging the integrity of the intestinal tight junctions. A1136-37.

As set forth below, clear factual errors in the district court's decision reveal its reliance on hindsight to ignore this prior art. "In other words, knowing that the inventor succeeded in making the patented invention," the district court "develop[ed] a hunch that the claimed invention was obvious, and then construct[ed] a selective version of the facts that confirms that hunch." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012).

A. The District Court Clearly Erred in Defining the Obviousness Inquiry Narrowly in Terms of the Solution Claimed in the Invention.

The asserted claims recite the first oral dosage formulation for the treatment of osteoporosis to achieve PEA. *See supra* p. 19. Yet in framing the obviousness inquiry, the district court assumed PEA and asked simply "was it obvious to use EDTA only as a calcium blocking agent to defeat the food effect…." A3. With this improperly narrow framing, the district court found the asserted claims' specific solution combining 100 mg of EDTA with 35 mg of risedronate for release in the small intestine to achieve PEA an obvious development. A19-20, 32, 50-64. In thus "us[ing] the invention to define the problem that the invention solves," the district court erred. *Mintz*, 679 F.3d at 1377.

The effect of this initial error is plain. "[A]n overly narrow 'statement of the problem [can] represent[] a form of prohibited reliance on hindsight, [because]

[o]ften the inventive contribution lies in defining the problem in a new revelatory way.'" *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (quotation omitted). Here, for example, the inventors' "revelatory" identification of the problem actually led them to coin a new term—PEA—for absorption that "is similar with or without food." *See* '459 patent, 4:59-67 (A76).

Moreover, "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Insite Vision*, 783 F.3d at 859 (quotation omitted). By starting its analysis with the solution, the district court was able to select passages from the prior art in order to reconstruct the claimed ingredients and doses from prior art references that proposed a wide range of chelators, bisphosphonates, and delivery formulations, and for decades cautioned *against* clinical use of EDTA. *See supra* pp. 10-11, 20. Having set out in search of the claimed invention, it is neither surprising nor defensible that the district court found it. *See Mintz*, 679 F.3d at 1377 ("[W]hen someone is presented with the identical problem and told to make the patented invention, it often becomes virtually certain that the artisan will succeed in making the invention.").

B. The District Court Clearly Erred in Assessing the Prior Art.

The district court's selective use of the prior art is evident in its disregard of the PTO's review of the '459 and '460 patents. Although "[i]t is difficult to imagine a patent law suit in which an accused infringer is unable to add some new

'pertinent' art," *W.L. Gore*, 721 F.2d at 1553, that was not considered by the PTO, this is such a lawsuit. The Examiner considered all of the principal—and nearly every—reference relied upon by Teva and the district court. *Compare*, *e.g.*, A3 n.2 *and* A268-70 *with* '459 patent, 1-2 (A75) *and* '460 patent, 1-2 (A103). In these circumstances, an obviousness finding faces "the added burden of overcoming the deference that is due to a qualified government agency presumed to have done its job." *Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) (quotation omitted). *See also Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2250-51 (2011). The district court's decision cannot surmount this hurdle.

The district court concluded that a person of ordinary skill could have *elected* to "use EDTA solely as a chelator to bind calcium" and not as a permeability enhancer spreading the tight junctions. A58. *See also* A2, 9, 37, 40, 65. For this reason, the district court discounted the sections within prior art references warning against clinical use of EDTA due to its potential impact on the tight junctions. *See* A37. But the district court's assessment of the EDTA prior art fundamentally misunderstands how EDTA works. It does not operate separately through "two mechanisms." A2. Rather, EDTA enhances permeability and threatens the tight junctions, which are composed of calcium and other metal ions, *precisely because* it is a chelator. *See supra* pp. 10-11.

No expert disputed this basic science or that EDTA enhances the permeability of the intestinal wall at some dose. Dr. Yates, for example, conceded that an ordinarily skilled artisan would not know when that point would be reached in a given patient. *See* A572, 76-79. The primary reference used by the district court, BR '601, indicates that permeability enhancement will occur at a 20 mg dose of EDTA. *See* A1624-25 (explaining that invention "increases the permeability of the intestinal mucosa"); A1627 (describing method to calculate dose of chelating agent); A495 (calculating BR '601 range of 20 to 175 mg of EDTA).

In addition to ignoring the teaching of its primary reference, the district court elsewhere contradicted its own finding that EDTA may function separately as either a chelator or as permeation enhancer. *See* A17, 23 (acknowledging that PEA requires an EDTA dose high enough to increase bisphosphonate absorption, but low enough not to harm tight junctions). The district court's decision thus rests on either an unsupported or inconsistent finding. Either is clear error. *See, e.g.*, *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."); *Scanner Techs. Corp. v. Icos Vision Sys. Corp. N.V.*, 528 F.3d 1365, 1378 (Fed. Cir. 2008) (factual finding may be clear error where "internally inconsistent").

Given this fundamental error, the district court's decision cannot overcome the presumption of patent validity. 35 U.S.C. § 282. *See also Mintz*, 679 F.3d at 1377 (noting "prior art may have different probative weight for…prior consideration before the PTO"); *Sciele Pharma*, 684 F.3d at 1260 ("[T]he fact that references were previously before the PTO goes to the weight the court…might assign to the proffered evidence….").[17]

C. The District Court Clearly Erred in Its Comparison of the Prior Art to the Claimed Invention.

The district court's comparison of "the differences between the claims and the prior art," *Kinetic Concepts*, 688 F.3d at 1360, fares no better. In each element of its analysis, the district court "disregard[ed] disclosures in the [prior art] that diverge from and teach away from the invention in hand." *W.L. Gore*, 721 F.2d at 1550. *See also Genetics Inst., LLC v. Novartis Vaccines & Diagnostics*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) ("A prior art [reference] must be considered in its entirety, i.e., as a *whole*, including portions that would lead away from the invention in suit." (quotation omitted)). In so doing, the district court used "hindsight reconstruction to pick and choose among isolated disclosures in the

[17] The district court appeared to doubt the validity of the PTO's review. *See* A445-46 (Counsel: "[T]he patent office is supposed to be reviewing the claims under the statute, rejecting them if they don't meet. THE COURT: I understand. But the key words being supposed to be.").

prior art to deprecate the claimed invention." *In re Fritch*, 972 F.2d at 1266 (quotation and alteration omitted).

1. BR '601 Does Not Disclose the Claimed Formulation.

The district court determined that BR '601 discloses the claimed formulation because it broadly discloses a formulation from a laundry list of different bisphosphonates (including risedronate), chelating agents (including EDTA), and release agents (including an enteric coating). *See* A14-20; A1623, 1626-27. That finding cannot withstand scrutiny.

The district court first concluded that BR '601's reference to selecting a bisphosphonate dose with "a time interval, effective quantity, and rate of release depending on the disease to be treated and as known to a person skilled in the art"—ellipsized by the district court to "effective quantity…known to a person skilled in the art"—"explicitly suggested" using a bisphosphonate dose already in use, which would include the 35 mg weekly dose of risedronate used in Actonel. A16. Further, the district court reasoned that BR '601 "did not *suggest* using less than the known 'effective quantity' of the bisphosphonate." A16 (emphasis added).

But the district court did not acknowledge that, according to this reading, 35 mg of risedronate would be an "acceptable choice" for all bisphosphonate formulations: whether administered "at regular intervals…or irregular intervals,"

as an immediate release formulation or as a delayed release formulation. A1628. Nor did it explain why a POSA would thus believe the same dose would be effective under all circumstances. Nor did the district court attempt to harmonize its conclusion that BR '601 did not even *suggest* using less than the known "effective quantity" of the bisphosphonate with the *expressly stated* goal of the invention to reduce the bisphosphonate dose "compared to the current treatment." A1625. *See also* A1623; *supra* p. 21. The district court thus committed clear error: even if the POSA would have considered using the 35 mg dose used in Actonel, that person would have lowered the dose as instructed by BR '601.

The district court further determined that BR '601 disclosed an EDTA dose range between 20 and 175 mg that renders the claimed formulation obvious because the claimed 100 mg EDTA dose is not critical to the invention. A15-16, 52. Neither the law nor the record support this conclusion.

As a matter of law, the authorities relied upon by the district court in finding BR '601's broad ranges sufficient to render the claimed invention obvious, A52, are inapplicable where the prior art's "disclosed range is so broad as to encompass a very large number of possible distinct compositions." *In re Peterson*, 315 F.3d 1325, 1330 n.1 (Fed. Cir. 2003). Here, BR '601 identifies numerous bisphosphonates (12), chelating agents (4), and release agents (6) to be combined, and, if 35 mg of risedronate is selected and the chelator is EDTA, a "preferable but

not exclusively preferable" EDTA dose range from 20 to 175 mg (a spread of 155 mg). A1623, 1626-27. *See supra* pp. 21-22, 34. Those variables result in thousands of possible combinations.[18] *Compare Genetics Inst.*, 655 F.3d at 1306 (finding that obviousness could not be based on prior art range encompassing "about 68,000 protein variants") *with Iron Grip Barbell Co., Inc.. v. USA Sports, Inc.*, 392 F.3d 1317, 1321-22 (Fed. Cir. 2004) (finding range of three variants rendered invention within the range obvious).[19]

As a matter of fact, because the EDTA range that the district court found in BR '601 is derived from the bisphosphonate dose erroneously selected by the district court, *see supra* pp. 21-22, it was, by extension, also clear error to find that BR '601 disclosed the 20-175 mg range. Moreover, even assuming that the range itself was not calculated in error, "that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."

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[18] Those possibilities are compounded by the fact that BR '601 discloses only a vague range—and an "effective quantity"—for its bisphosphonate dose. *See* A1623.

[19] The district court's reliance on *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989), is similarly misplaced. "In *Merck*, one reference expressly taught the combination of the compounds claimed in the patent," *Insite Vision*, 783 F.3d at 863, revealing only 1200 potential combinations. In *Merck*, moreover, those combinations were aimed at "the identical purpose" as the patent at issue. *Merck*, 874 F.2d at 807. BR '601, by contrast, teaches "increas[ing] the permeability of the intestinal mucosa," A1625, that the inventors sought to avoid. *See supra* pp. 11-12.

In re Baird, 16 F.3d 380, 382 (Fed. Cir. 1994). Instead, a patentee may overcome an asserted overlap in ranges "by showing that the claimed [value] is critical," or "that the prior art teaches away from the claimed invention in any material respect." *In re Peterson*, 315 F.3d at 1330-31. Both conditions are met here.

a) *The prior art taught away from the claimed invention.*

The prior art repeatedly "disparage[d] or otherwise discourage[d] the use" of EDTA in clinical applications. *Id*. at 1332. For decades, researchers studying the impact of EDTA on bisphosphonate absorption concluded variously that EDTA was "unsuitable for clinical use," "inappropriate," "limited," and had "damaging effects on mucosal integrity." *See supra* pp. 10-11. Contrary to the district court's suggestion, these references did not restrict their EDTA warnings to "high doses," A37, and, indeed, do not always refer to any EDTA dose, *see* A3758. The references draw no distinction that can support the district court's vague line-drawing between "high" and "low" doses of EDTA.[20]

Seen in this context, moreover, BR '601 itself teaches away from selecting 100 mg of EDTA "by focusing on" enhancing absorption in order to decrease the dose of bisphosphonate. *In re Baird*, 16 F.3d at 382. *See* A1624-25. BR '601 proposed to achieve that result by, *inter alia*, increasing intestinal permeability (a

[20] The district court's conclusion also rested on its erroneous premise that EDTA can be used separately "as a chelator of calcium and as a permeability enhancer." A36-37; *supra* pp. 32-34.

result elsewhere considered something to be avoided) at low doses: for 35 mg risedronate, as low in a "preferable" embodiment, as 20 mg of EDTA. A1625. Because the district court ignored this key aspect of its primary reference, *see* A32-34, it "failed to consider the [BR '601] reference in its entirety and thereby ignored those portions of the reference that argued against obviousness." *Bausch & Lomb*, 796 F.2d at 448.[21] Taken as a whole, the prior art indicated that the claimed invention would be "dangerous to the patient," and thereby taught away from the inventors' innovation. *Kinetic Concepts*, 688 F.3d at 1362.

The district court discounted this overwhelming evidence teaching away from the claimed invention by pointing to (1) Poiger's use of a 250 mg EDTA dose, A39, 53, and (2) post-invention statements made by P&G to obtain FDA approval of its clinical trials, A39-40. Neither justification withstands scrutiny.

First, as Dr. Yates conceded, Poiger—a study of tetracycline absorption in five individuals that did not consider long-term side effects—showed that EDTA is poorly tolerated by "neutraliz[ing]" the dose of EDTA with either sodium hydroxide or the tetrasodium salt of EDTA to avoid gastrointestinal irritation from EDTA shown in other studies. A1610. *See also* A584-85. Nor did Dr. Yates, *see*

[21] The district court's blindness was selective. Elsewhere, the district court acknowledged BR '601's goal to increase intestinal permeability. A55. The district court thus erred by selectively "choos[ing] among isolated disclosures in the prior art to deprecate the claimed invention." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) (quotation omitted)).

supra pp. 23-24, or the district court, A39, 53, explain why a POSA would rely on Poiger's "neutaliz[ed]" concoction rather than heed conflicting results of two other studies showing gastrointestinal irritation from the "disodium salt of EDTA," A1610, that is used in the claimed invention. Indeed, Poiger published in 1978 and concluded by suggesting "further consideration" of EDTA administration. A1610. Over the subsequent 27 years before the invention, that further consideration was given and taught against administration of EDTA. *See supra*. Reliance on Poiger in these circumstances "suggests…a resort to hindsight." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013) (explaining that elapsed time between prior art and patent filing date indicates lack of obviousness).

Second, [redacted]

[redacted] *Compare* A3867-3948 *with* A1371-1576. P&G's resulting closely monitored tests of the EDTA dose in humans, A1145-48, concluded before the 2004 communication that the district court relied on to find that Warner Chilcott admitted EDTA's safety to the FDA, *see* A857 (citing A605-07). With their initial tests complete, the inventors did not stand in the shoes of a POSA, and their path going forward is not relevant to obviousness. *See* 35 U.S.C. § 103.

Moreover, the district court's reliance on P&G's statements to the FDA is internally contradictory. In support of its clinical trials, P&G advocated a

particular view on, *inter alia*, literature describing EDTA's use in food additives, A1380, 1392, that the district court (correctly) found unpersuasive because a food additive is administered with food (including calcium) to which the EDTA can pre-chelate long before reaching the lower gastrointestinal tract. A36. The district court's "about-face[]"—relying on P&G statements to FDA arguing that food additive literature supports EDTA safety for clinical testing on the one hand and, on the other hand, dismissing Teva's argument that food additive literature demonstrates EDTA safety—is clear error. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (reversing district court's "internally inconsistent" decision under Section 112); *see also In re Fay*, 347 F.2d 597, 603 (C.C.P.A. 1965) (board decision erroneous where internally inconsistent).

b) *The claimed EDTA dose is critical.*

The district court also erred in finding the claimed 100 mg EDTA dose was not critical to the claimed formulation. A18-19. Because the patents-in-suit claim a formulation, it is "improper to focus only on the dosage of [one component] in isolation." *Avanir Pharm., Inc. v. Actavis S. Atlantic, LLC*, 36 F. Supp. 3d 475, 499 (D. Del. 2014) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)). The district court, however, discounted the claimed formulation by concluding that the doses of risedronate and EDTA "work independently of each

other and are not interdependent." A18-19. Again, the district court's conclusion cannot be squared with the prior art on which it relied.

BR '601 treats the doses of bisphosphonate and EDTA as interdependent, defining the amount of chelating agent necessary to enhance absorption in "proportion" to the administered dose of bisphosphonate. A1627; *see also* '459 patent, 9:9-15 (A79) (same). In fact, BR '601's ratio of chelating agent-to-bisphosphonate provides the means used to calculate the preferable EDTA dose range—20 to 175 mg—that the district court relied on in finding the claimed invention obvious. *See* A495. And that calculation is itself dependent upon choosing, at the outset, 35 mg of risedronate as the bisphosphonate dose. *See* A604-05. The district court thus continued to pick and ignore teachings from the same reference to "construct[] a selective version of the facts that confirms [its] hunch" that the invention was obvious. *In re Cyclobenzaprine*, 676 F.3d at 1079.

The district court's resort to the '459 and '460 specifications to "confirm" lack of criticality, A19-20, does not salvage the judgment. In the district court's view, the specifications demonstrate that a 100 mg dose of EDTA is not critical because the specifications include examples of a wide range of EDTA doses that purport to implement the invention. A20-21. But the mere presence of unsupported statements in the specifications suggesting the use of broader ranges of EDTA does not establish efficacy when there is "no indication that one skilled

in the art would accept without question the statements as to the effects of the claimed drug products and no evidence has been presented to demonstrate that the claimed products do have those effects." *Rasmusson v. SmithKline Beecham corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005). Indeed, it is well-established that a specification may include merely "prophetic" examples. *See*, *e.g.*, *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1189 (Fed. Cir. 2014) ("[A] patent does not need to guarantee that the invention works for the claim to be enabled."); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1357 (Fed. Cir. 2010) ("Prophetic examples are routinely used in the chemical arts, and they certainly can be sufficient to satisfy the written description requirement.").

For that reason, obviousness often depends on the existence in the prior art of data from which an ordinarily skilled artisan "could compute" the relevant limitation. *See Sciele Pharma*, 684 F.3d at 1260. *See also Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737 (Fed. Cir. 2014); *Ortho-McNeil*, 344 F. App'x at 600 (relying on data in the specification of the patent-in-suit). Here, a skilled artisan at the time of the invention would not have "accepted without question," *Rasmusson*, 413 F.3d at 1323, that all doses of EDTA disclosed in the specifications would increase bisphosphonate absorption without increasing intestinal permeability. To the contrary, the prior art either explicitly cautioned

against clinical use of EDTA, *see supra* pp. 10-11, or, in the instance of BR '601, offered no data assessing success within its claimed ranges, *see* A1621-33.

Indeed, experts on both sides—and the district court itself, A25—acknowledged that test results are necessary to demonstrate achievement of PEA. *See, e.g.*, A1219-20 ("We would have to do a food effect study" to show PEA); A515-18 (relying on Poiger test data to argue that it demonstrates PEA). The test results in the record support the criticality of the claimed 100 mg EDTA dose: (1) the Atelvia formulation succeeded with a 100 mg dose; (2) a second P&G formulation also succeeded using a 100 mg dose, *see* A1223; and (3) [redacted] A3785. *See Genetics Inst.*, 655 F.3d at 1307-09 (relying on post-filing data demonstrating unexpected results of claimed invention).[22] There is no evidence that any dose other than 100 mg achieves PEA.

Thus, the district court erred in finding the bare inclusion of broader ranges of EDTA in the '459 and '460 specifications sufficient to conclude that all values

[22] Teva's contemporaneous documents belie the district court's disregard of Teva's failures on the ground that they were unexplained. A20. The district court's conclusory dismissal lacks the "articulated reasoning with some rational underpinning" necessary "to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d at 988.

of EDTA would work. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) (noting that patent-in-suit "did not disclose experimental data or test results for any of these compounds"). Instead, "the evidence showed that a person of ordinary skill in the art would have expected the…[formulation] to operate differently, or not at all, outside of the" claimed 100 mg dose. *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015).

2. Poiger Does Not Disclose PEA.

Having found that its lead reference—BR '601—fails to disclose PEA, A25, the district court relied on Poiger, which it found to be "powerful evidence for a skilled artisan" to graft PEA onto BR '601. A61. That reliance was misplaced.

Poiger did not show PEA because it does not provide any information about what happens when the same doses of tetracycline and EDTA are administered in a fasted state as compared to a fed state. All patients fasted before engaging in any of the experiments, A1608, and Poiger did not compare any subject who took the same amount of tetracycline and EDTA with and without milk. A1608. Poiger therefore provides no information about whether similar absorption of a bisphosphonate would occur when administered with EDTA in a fasted state or a in fed state, in which—as Dr. Yates and Warner Chilcott's toxicologist, Dr. Rodricks, agreed, *see* A706-07, 716-18; A572, 576-79—the amount of metal ions

available in the portion of the gastrointestinal tract where the EDTA would release is not predictable.[23]

And while Poiger reports that by "[u]sing a combination of EDTA and [tetracycline] the bioavailability of the drug remained constant irrespective of the diet," A1610, this conclusion was premised—as Dr. Yates conceded—on selecting an EDTA dose to match the amount of calcium ions in the milk administered, A1609; A516. This "neutaliz[ed]" both the milk and the danger that excess EDTA would be free to chelate the metal ions in the tight junctions. A535.

Because it carefully controlled the amount of calcium and other metal ions present in the gastrointestinal tract of the five patients by (1) having them fast before participating in the study, and then by (2) matching the EDTA with the calcium ions in the milk in the lone experiment in which milk was administered with EDTA, *see* A1609 (describing Experiment 4), Poiger provides no information about how to achieve PEA with a bisphosphonate formulation in the real world. Certainly it provides no information about how to achieve PEA in a bisphosphonate formulation intended for a wide variety of patients—"the problem

[23] Mahé is not to the contrary. A59. That study employed an artificial delivery technique and a "high calcium" meal of skim milk that would not tell a skilled artisan how a normal oral dosage form would perform or the amount of calcium that would be present at the site of release. *See* A567-69; A1668-69. Mahé's results were also inconsistent with other studies, A1672; A568-69, and the district court gave no reason that a skilled artisan would follow the former and not the latter. A59-60.

confronting the inventor[s]"—as opposed to the five subjects in the Poiger study. *See Bancorp Servs., LLC v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1375 (Fed. Cir. 2004). Thus, the district court clearly erred in finding that Poiger taught PEA.

This clear error is further evident in Poiger's treatment of Experiment 4's administration of EDTA in solution with milk and tetracycline. While the district court relied on Experiment 4—in which the EDTA dose was selected to match the co-administered calcium ions in the milk—as the example of administration in a fed state and evidence of PEA, A31, its treatment of Experiment 4 cannot be squared with its treatment of the food additive literature, which it (correctly) dismissed as unpersuasive. A36. In both instances, the EDTA was effectively pre-chelated. Such internal inconsistency amounts to clear error. *See*, *e.g.*, *Scanner Techs.*, 528 F.3d at 1378; *Hybritech*, 802 F.2d at 1384; *In re Fay*, 347 F.2d at 603.

Finally, Poiger's results do not square with BR '601. While Poiger showed that "[w]hen [tetracycline] was taken simultaneously with EDTA, no significant change in [tetracycline] absorption was observed compared to the control experiment, in which [tetracycline] was taken only with water," A1609, the result is directly contrary to the promise of BR '601, made years after the Poiger reference was published, that EDTA would increase absorption by increasing intestinal permeability even when given at low doses. *See supra*; *Leo Pharm.*, 726 F.3d at 1356. Indeed, Poiger itself conceded that its results differed from two other

studies, one "who found reduced" and another "who reported increased absorption of [tetracycline] in presence of EDTA." A1609. Neither the district court nor Dr. Yates, *see supra* pp. 40-41, gave any reason for crediting Poiger's results, or for determining that Poiger would provide a POSA with a reasonable expectation of success, in light of the conflicting studies.[24] *See, e.g.*, *In re Cyclobenzaprine*, 676 F.3d at 1068-69 (party challenging validity "must demonstrate by clear and convincing evidence…that the [POSA] would have had a reasonable expectation of success" in achieving the invention).

D. The District Court Clearly Erred in Finding a Motivation to Modify BR '601.

The party asserting obviousness "must demonstrate by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention…." *In re Cyclobenzaprine*, 676 F.3d at 1068-69. This Court has recently reiterated that "[a] reason for combining disparate prior art references is a critical component of an

[24] While the district court's discussion of PEA focuses on Poiger, A61, the district court also briefly refers to WO '111 as a source of PEA, A30, 56-57. WO '111 sets as its goal "increase[d] absorption," A520, and suggests only that its formulations can be given "together with food intake," A1637, not that it achieves similar absorption in the fed and fasted states. The district court's selection of a few stray lines from WO '111 is therefore unconvincing. *See Bausch & Lomb*, 796 F.2d at 448 (district court erred in "select[ing] a single line out of" prior art reference).

obviousness analysis…." *InTouch Techs., Inc. v. VGO Communications, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014). That component is lacking in this case.

The district court considered whether a skilled artisan would have a reason "to modify" BR '601—in which it found the claimed physical ingredients in combination—with Poiger—the district court's source of PEA. A3, 57-61. But "[e]ven if the references disclosed all of the limitations of the asserted claims, which they do not, [Teva] still needed to proffer evidence indicating why a person having ordinary skill in the art would combine the references to arrive at the claimed invention." *Kinetic Concepts*, 688 F.3d at 1366. Teva did not provide that evidence.

Expert testimony of motivation is necessary where, as here, "the technology at issue…is not the type of technology where common sense would provide the motivation to combine…references." *Kinetic Concepts*, 688 F.3d at 1369. *See also Wyers v. Master Lock Co.*, 616 F.3d 1231, 1240 n.5 (Fed. Cir. 2010). Conclusory or vague expert testimony, however, is legally insufficient. *See*, *e.g.*, *Whitserve, LLC v. Computer Packages, Inc.*, 694 F.3d 10, 24 (Fed. Cir. 2012); Instead, an expert must "provide the necessary articulated reasoning with some rational underpinning to support a conclusion of invalidity based on [alleged] combinations." *InTouch Techs.*, 751 F.3d at 1351, 1352 (quotation omitted).

Teva's experts "failed to provide the glue to combine" BR '601 and Poiger. *Id*. at 1348. Dr. Yates opined only that a skilled artisan

> would have been motivated [to combine the prior art references] because the prior art clearly taught that you could overcome the food effect with the delayed-release formulation of a risedronate with EDTA. And they would have been motivated to do so because some patients clearly would prefer to take the drug with or without food.

A537-38. Such conclusory statements, which do not even address motivation to achieve PEA (an element that is much more than being able to take the drug with food), provide no specific reason for modifying BR '601 to add features supposedly disclosed in Poiger, let alone to combine references to "solve a problem which persisted in the art…." *In re Newell*, 891 F.2d 899, 902 (Fed. Cir. 1989) (quotation omitted). *See supra* pp. 9-10, 16-17.

The references themselves do not make up the shortfall in Teva's expert testimony. BR '601 seeks to reduce bisphosphonate doses by, among other things, "increas[ing] the permeability of the intestinal mucosa," A1625, with an EDTA dose as low as 20 mg, in direct conflict with the goals of the invention, *see supra* pp. 11-12, and the warnings of the prior art against increasing intestinal permeability, *see supra* pp. 10-11. Accordingly, BR '601 "lacks any suggestion or incentive" to use its disclosures to achieve PEA, *In re Fritch*, 972 F.2d at 1265, which was not an "objective of the project," *InTouch Techs.*, 751 F.3d at 1350.

In contrast, the district court reasoned that Poiger teaches both PEA and that increased permeability does not occur until much higher doses of EDTA are used. *See* A30-32, 39, 53, 57-58. Instead of positing a motivation to *modify* BR '601, the district court in effect concluded that the POSA would have concluded from the 1976 Poiger reference that BR '601, published years later, was wrong, retained the "correct" aspects of BR '601 and replaced "incorrect" portions with what supposedly can be gleaned from Poiger. "Such conflicting teachings cannot reasonably be viewed as suggesting their combination…." *Karsten Mnfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001) (explaining that two references combined by district court "are directly opposing"). Only the "hindsight knowledge" of the claimed invention would lead a skilled artisan "to select and combine these [conflicting] parts" of BR '601 and Poiger. *Id.*

The district court accordingly erred in failing to consider the mutually "discrediting effect" of the references. *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991). *See also W.L. Gore*, 721 F.2d at 1551 (finding district court erred in ignoring "clear divergence" between references it sought to combine).

* * *

Taken as a whole, it is clear that the district court used its hindsight knowledge of the inventors' success to, among other things, excise conflicting teachings from its primary reference, BR '601, and replace those with elements

from a study by Poiger that predates BR '601 by 25 years. Indeed, the district court did not explain *how* the POSA would have modified the controlled release formulation disclosed in BR '601 to achieve PEA, but simply that "[t]he totality of the evidence establishes a motivation to modify the [BR '601] to include the ***limitation*** 'pharmaceutically effective absorption.'" A58 (emphasis added). Of course, the question is whether the POSA would have been led to the claimed invention, not whether such a person would have added "limitations" to arrive at patent claims. In other words, the inventors' "claims were used as a frame, and individual, naked parts of separate prior art references were employed as a mosaic to recreate a facsimile of the claimed invention," *W.L. Gore*, 721 F.2d at 1552, in the face of conflicting prior art. The district court's resulting judgment should be reversed.

II. The District Court Erred as a Matter of Law by Dismissing Unrefuted Objective Evidence of Nonobviousness.

"This court has repeatedly emphasized that the objective indicia constitute independent evidence of nonobviousness" and "may often establish that an invention appearing to have been obvious in light of the prior art was not." *Mintz*, 679 F.3d at 1378 (quotation omitted). These objective indicia play a critical role in "the difficult task of avoiding subconscious reliance on hindsight," *id*, and accordingly, "must always when present be considered en route to a determination of obviousness." *In re Cyclobenzaprine*, 676 F.3d at 1075 (quotation omitted).

Warner Chilcott presented overwhelming objective evidence, largely from Teva's own witnesses and documents, demonstrating industry skepticism, failure of others, and copying of the invention, all of which belie a finding of obviousness. The district court erred as a matter of law by dismissing undisputed objective evidence, *see id*. at 1079, and, to the extent it considered such evidence, fell "into the…improper trap of constructing a selective version of the facts relating to the objective considerations so as to confirm its hunch that the asserted claims were obvious." *Id*. at 1080.

A. Teva Failed to Rebut Warner Chilcott's Overwhelming Objective Evidence.

"The objective indicia of nonobviousness serve a particularly important role in a case, like this one, where there is a battle of scientific experts regarding the obviousness of the invention. In such a case, the objective indicia provide an unbiased indication regarding the credibility of that evidence." *Kinetic Concepts*, 688 F.3d at 1370-71. *See also Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc.*, 21 F.3d 1068, 1072 (Fed. Cir. 1994). Like the district court, an expert asserting obviousness must consider objective evidence. *See InTouch Techs.*, 751 F.3d at 1348.

But Teva's experts made little "effort…to guard against…hindsight bias by appropriately considering ***all*** objective evidence of nonobviousness." *Id*. at 1352 (emphasis added). To the contrary, Dr. Yates testified only with respect to the

long-felt need for the claimed invention and an alleged simultaneous invention. *See, e.g.*, A876-78. "By failing to account for objective evidence of nonobviousness," Dr. Yates's "analysis was incomplete, and ultimately insufficient to establish obviousness by clear and convincing evidence." *InTouch Techs.*, 751 F.3d at 1352. *See also id*. at 1354.[25]

B. The District Court Erred in Dismissing Unrefuted Evidence of Teva's Failure to Achieve the Claimed Invention and in Failing to Properly Weigh Evidence of Long-Felt Need.

"Evidence that others tried but failed to develop a claimed invention may carry significant weight in an obviousness inquiry" and "could be determinative." *In re Cyclobenzaprine*, 676 F.3d at 1081 (quotation omitted). In this case, unrefuted evidence at trial showed that Teva's scientists failed to achieve PEA with a bisphosphonate-EDTA formulation containing 40 mg EDTA. *See supra* pp. 17-19. [redacted] A3785. Teva also experimented with chelators other than EDTA, A1043-44, to no avail.

"[T]here can be little better evidence negating an expectation of success than actual reports of failure." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-*

[25] Where an expert, like Dr. Yates here, A554, "purports to testify…to the ultimate question of obviousness, the expert must consider all factors relevant to that ultimate question." *InTouch Techs.*, 751 F.3d at 1352 n.8.

Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir. 2003). Indeed, "[w]here, as here, the obviousness determination turns on whether one of ordinary skill in the art would have expected that a particular formulation of…[a drug] would be successful—in other words, would render a therapeutically effective treatment—objective indicia of failure of others and longfelt need are particularly telling." *In re Cyclobenzaprine*, 676 F.3d at 1083. The district court failed to listen.

While the district court acknowledged Teva's failures, A49, it failed to weigh this telling evidence as indicative of "failure of others" in assessing obviousness, A66. Instead, the district court dismissed without explanation Teva's failure to achieve PEA with a 40 mg EDTA dose. A49. That failure, however, falls directly within BR '601's range of EDTA doses, upon which the district court otherwise relied heavily.

And while the district court separately explained Teva's failure to test "its 100 mg EDTA batch in humans" until after Atelvia's launch as the product of "constraints in funding," A49-50, that rationale lacks any support in the record. The district court's sole citation makes no mention of costs or Teva's 100 mg formulation. A50 (citing A1045). The district court thus clearly erred. *See In re Kahn*, 441 F.3d at 988 (requiring "some rational underpinning to support the legal conclusion of obviousness"); *In re Cyclobenzaprine*, 676 F.3d at 1082 (error to "disregard[]…failures").

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Shorn of the district court's unsupported dismissal, Teva's "failure to develop" the patented invention "strongly supports a nonobviousness finding," *id*. at 1081, particularly given that its failures occurred ***after*** the '459 and '460 patents issued in January 2010. Indeed, [redacted] A3786. That sequence of events "show[s] indirectly the presence of a significant defect in the prior art…." *In re Cyclobenzaprine*, 676 F.3d at 1082 (quotation omitted). That defect is clear—the prior art taught away from the claimed invention. *See supra* pp. 39-40; *infra* pp. 58-59.

"Longfelt need is closely related to the failure of others." *In re Cyclobenzaprine*, 676 F.3d at 1082. Although the district court found "some" long-felt need to eliminate the food effect and, at the same time, poor patient compliance, A43, its weighting was insufficient. These problems persisted for decades, even after the weekly and monthly dosing treatments that the market first tried to remedy the problem, *see* A476-77; A1637 ("[A] solution to the problems associated with the poor and variable absorption of orally administered bisphosphonates known for a long time has not yet been found."); *supra* pp. 9-10, 16-17.

The claimed formulation "didn't just solve the issue about compliance with the dosing rules, it made those rules not be even an issue anymore." A956. Such evidence is particularly probative in this case, *see In re Cyclobenzaprine*, 676 F.3d

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at 1083 (relying on evidence that predecessor "formulation existed for decades, but…led to poor patient compliance"), and further weighted by the related evidence of Teva's failures, *see id*. at 1082 ("Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried and failed to satisfy that demand.").

C. The District Court Erred in Dismissing Unrefuted Evidence of Industry Skepticism.

Objective evidence plays an important role by demonstrating "the contemporary view of the invention by competitors and the marketplace." *Spectralytics, Inc. v. Cordis Corp.*, 649 F.3d 1336, 1344 (Fed. Cir. 2011). The record evidence makes clear that, "even after reading" the issued patents, *Kinetic Concepts*, 688 F.3d at 1370, [redacted]

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[redacted] Teva did not conduct studies with a 100 mg EDTA dose until after Atelvia's approval on October 11, 2010. A1051.

The district court's dismissal of the Teva scientists' skepticism—on the ground that it purportedly was not clear the Teva scientists developing its generic product were skilled artisans, A48—further demonstrates the district court's use of internally inconsistent findings because the district court subsequently relied on these scientists to indicate the understanding of a skilled artisan, *see* A59-60. Such skepticism by Teva's Associate Director of Formulation R&D, internal toxicologist, and a manager of bioequivalent studies, *see supra* n.11, is relevant in assessing obviousness. *See Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1304-05 (Fed. Cir. 2010). The district court again erred by failing to weigh this evidence.

D. The District Court Erred in Crediting Evidence of Simultaneous Invention.

While dismissing unrefuted evidence of Teva's failure and failing to credit the skepticism expressed by Teva scientists about the invention, the district court found, and weighed heavily, that a patent application filed by Takeda indicated simultaneous invention of the claimed formulation. A45-48.

That the Takeda specification discussed an objective to obtain similar absorption in the fasted and fed states is irrelevant, however, because the question is what Takeda invented, not what its application disclosed as its scientific

objectives. Takeda's only evidence of PEA was with sodium citrate as a chelator, not EDTA. A1273-74; A1597-1602. Because Takeda's invention was not the same invention as that recited in the asserted claims, Takeda is not evidence of "simultaneous invention." *See The Procter & Gamble Co. v. Paragon Trade Brands, Inc.*, 989 F. Supp. 547, 595 (D. Del. 1997) (rejecting simultaneous invention argument where not "identical"). The district court erred in considering it evidence of simultaneous invention, but, in any event, it could not possibly outweigh the evidence of objective considerations proffered by Warner Chilcott.

E. The District Court Erred in Dismissing Unrefuted Evidence of Copying.

The district court likewise ignored evidence showing that Teva copied the claimed formulation. While the district court titled a section of its opinion "Failure of Others and Copying," A49, it addressed only Teva's efforts to make formulations with EDTA. It did not address the copying evidence proffered by Warner Chilcott: even though Teva was not required by FDA to use 100 mg EDTA—an inactive ingredient—in its generic product,[26] Teva copied both the type (EDTA) and amount (100 mg) of Atelvia's chelator exactly after considering other chelators and EDTA at other doses. *See supra* pp. 17-19. Teva's copying after Atelvia's market launch, on the heels of its failures to achieve PEA independently

[26] For this reason, the Court's decision in *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 983 (Fed. Cir. 2010), is inapplicable.

before Atelvia was approved, is powerful evidence of nonobviousness. *See Heidelberger*, 21 F.3d at 1072 ("[T]he litigation argument that an innovation is really quite ordinary carries diminished weight when offered by those who had tried and failed to solve the same problem, and then promptly adopted the solution that they are now denigrating.").

* * *

The district court's failure to weigh *all* objective evidence of nonobviousness constitutes a manifest error of law. *See In re Cyclobenzaprine*, 676 F.3d at 1075-76.

CONCLUSION

The Court should reverse the district court's judgment of invalidity, and remand the case to the district court for an entry of judgment against Teva for infringement of the '459 and '460 patents.

Dated: June 26, 2015

Respectfully submitted,

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ADDENDUM

FOR PUBLICATION **CLOSED**

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

WARNER CHILCOTT COMPANY, LLC, et al.,	Civil Case No. 11-6936 (FSH)
Plaintiffs,	
v.	**FINDINGS OF FACT AND CONCLUSIONS OF LAW**
TEVA PHARMACEUTICALS USA, INC.,	March 4, 2015
Defendant.	

HOCHBERG, District Judge:

This Opinion constitutes the Court's findings of facts and conclusions of law pursuant to Federal Rule of Civil Procedure 52.

I. INTRODUCTION

ATELVIA®—the osteoporosis drug covered by the challenged patents—purports to solve a problem experienced by patients who used earlier osteoporosis drugs: if the earlier drugs were taken with a meal, the active ingredient was captured by the calcium found in food molecules and was not absorbed into the body. [1] When the medicine failed to enter the bloodstream,

[1] Trial counsel for both parties, and the team of attorneys and staff supporting them, presented extraordinarily detailed chemistry with clarity and brevity. Each side presented only the most pertinent scientific points and condensed their arguments into a week-long presentation that the

patients' bones became susceptible to fractures. ATELVIA® addressed this "food effect" by combining the active ingredient risedronate with a calcium-blocking agent, EDTA, thus permitting patients to take the drug with a meal and still receive an effective dose.

It is uncontested that prior art disclosed combinations of the active ingredient and the calcium-blocking agent EDTA to increase absorption. The closest reference—the *Brazilian Application*—disclosed two mechanisms to increase absorption: (1) a process called chelation, where EDTA binds to calcium molecules in food and blocks them from capturing the active ingredient; and (2) permeability enhancement, where large doses of EDTA spread the pathways between intestinal cells, allowing more active ingredient to pass from the intestine into the bloodstream.

By binding to calcium ions in food, chelation increases absorption only when a patient has eaten a meal; absorption of the active ingredient is thus similar regardless of whether a patient has eaten or not. On the other hand, permeability enhancement amplifies overall absorption of any intestinal content. Increased intestinal permeability was viewed as harmful because other drugs or bacteria could also more easily pass into the bloodstream.

ATELVIA® employs only the first mechanism: it uses EDTA as a chelator to block the calcium in food, but not to enhance overall intestinal permeability. This achieves what the challenged patents call "pharmaceutically effective absorption," a limitation defined as similar absorption whether a patient has eaten or fasted. Fed exposure within about 50% of fasting

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Court was fully able to understand. They deserve a great deal of credit for their professionalism and judgment, conferring to narrow the areas of controversy so that judicial resources were expended only on resolving the heart of their dispute. The attorneys on both sides earned tremendous respect from all who watched, listened, and observed this trial.

exposure is expected to be "pharmaceutically effective absorption." Except for the "pharmaceutically effective absorption" limitation, the parties agree that the *Brazilian Application* contains "all of the elements of the asserted claim[s]." Thus, the main dispute is narrow: in light of the *Brazilian Application's* disclosure of EDTA's two mechanisms of absorption, whether it was obvious to modify the reference—using only the first disclosed mechanism of chelation and excluding the second disclosed mechanism of enhanced permeability—thus permitting a patient to take her osteoporosis medicine and receive a similar dose regardless of whether she has or has not eaten. In other words, was it obvious to use EDTA only as a calcium blocking agent to defeat the food effect, and would a skilled artisan have had a reasonable expectation of success in so doing?[2]

II. JURISDICTION

This Court has subject matter jurisdiction over this case pursuant to the patent laws of the United States and 28 U.S.C. §§ 1331, 1338, 1367, 2201 and 2202. Venue is proper in this District under 28 U.S.C. §§ 1391 and 1400(b). This Court has jurisdiction over the parties.

III. BACKGROUND

a. Procedural

Plaintiffs Warner Chilcott Co., LLC, and Warner Chilcott (US), LLC, (collectively "Plaintiffs" or "Warner") bring this patent infringement action against Teva Pharmaceuticals USA, Inc., ("Teva") under the Federal Food, Drug, and Cosmetics Act ("FFDCA"), and, more

[2] To answer this question, the Court also considers additional prior art, including the *Poiger Reference*, *WO '111*, the *Mahé Reference*, and the *Mitchell Reference*, and other relevant literature, including Lin, Janner, Ezra, Zakelj, Van Hoogdalem, Muranishi, and others.

specifically, the Hatch-Waxman Amendments to that law. Plaintiffs assert that two patents protect ATELVIA® from generic competition: U.S. Patent No. 7,645,459 (the "'459 patent") and U.S. Patent No. 7,645,460 (the "'460 patent"). Both patents describe a delayed-release formulation of the active ingredient risedronate in combination with ethylene diamine tetraacetic acid ("EDTA"). Warner acquired these patents when it purchased The Proctor & Gamble Company's pharmaceutical division in August 2009. (Joint Stipulation of Facts ¶ 3, Dkt. No. 270). Plaintiffs hold an approved New Drug Application ("NDA"), No. 22-560, under § 505(a) of the FFDCA, 21 U.S.C. § 355(a), for a delayed-release risedronate tablet formulation containing 35 mg of risedronate sodium and 100 mg of disodium EDTA, and marketed as ATELVIA®. (Joint Stipulation of Facts ¶¶ 5, 70, 71). These tablets were approved by the Federal Food and Drug Administration ("FDA") on October 8, 2010, and are promoted for the treatment of osteoporosis. (Joint Stipulation of Facts ¶ 69). Warner listed the '459, '460 patents and U.S. Patent No. 8,246,989 in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), in connection with ATELVIA®. (Joint Stipulation of Facts ¶ 77).

As required by 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Defendant Teva provided Plaintiffs with a "paragraph IV certification," notifying Plaintiffs that they had submitted an Abbreviated New Drug Application ("ANDA"), No. 20-3217, to FDA seeking approval to manufacture and market generic versions of ATELVIA® before the expiration of the '460 and '459 patents. Warner brought this patent infringement action against Teva within the forty-five day statutory period, filing a Complaint against the Defendant. Teva asserted counterclaims, seeking a finding that the challenged patents are invalid. Warner also filed patent infringement actions against the

pharmaceutical companies Watson Laboratories, Ranbaxy, and Impax Laboratories, asserting these same patents. The Watson, Ranbaxy, and Impax actions were each resolved by settlement.

In its case against Teva, Warner has dropped all asserted claims of U.S. Patent No. 8,246,989, and all asserted claims of the '459 and '460 patents except for claim 16 of the '459 patent and claim 20 of the '460 patent. Teva has stipulated to infringement of these claims. (Joint Stipulation of Facts ¶ 40). A bench trial was held regarding the validity of claim 16 of the '459 patent and claim 20 of the '460 patent.

b. Technology At Issue

The challenged patents claim an active ingredient called risedronate sodium. This drug is a member of a class called bisphosphonates, which have been used for decades to treat osteoporosis. This active ingredient is combined with an inactive ingredient called disodium EDTA, which chelates—or binds—metal ions in food, blocking them from capturing the active ingredient when a patient has eaten.

1. Bisphosphonates

Bisphosphonates have been used since the 1980s to treat osteoporosis and Paget's disease. (Trial Tr. 1A.100:16-25).[3] These diseases are characterized by a weakening of the bone. In a healthy human body, bone tissue is continually regenerated in an equilibrium of bone growth and bone disintegration. (Tr. 1A.103:14-104:9). Osteoblasts, a type of cell that builds new bone,

[3] Where the court reporter numbered the trial transcript with volume numbers, those volume numbers are used herein. Where the alternate court reporter dated, but did not number the trial transcript, the Court refers to the unnumbered trial transcript volumes as follows: July 14, 2014 P.M. Trial Tr. (hereinafter "Tr. 1B"); July 15, 2014 A.M. Trial Tr. (hereinafter "Tr. 2A"); and July 16, 2014 A.M. Trial Tr. (hereinafter "Tr. 3A").

are balanced by osteoclasts, a type of cell that destroys bone in a process called resorption. (*Id.*; Joint Stipulation of Facts ¶¶ 84, 85). In patients with osteoporosis, this normal balance is disrupted and bone resorption exceeds bone growth, leading to lower bone mass and a higher chance of fracture. (Tr. 1A.104:1-6).

Bisphosphonates have a strong affinity for the calcium crystals in bone, binding tightly to bone surfaces. (Tr. 1A.104:10-17). When a bone-destroying osteoclast engulfs a bone particle that is attached to a molecule of bisphosphonate, the osteoclast cell becomes less active or is destroyed. (*Id.*; PTX 135, at 176).[4] Consequently, bisphosphonates inhibit bone resorption. (DTX 167, at 280). Over time, the administration of bisphosphonates results in less active bone-destroying osteoclasts, less resorption, and more bone tissue. (Tr. 1A.104:15-24). Many pharmaceutical companies have developed species of bisphosphonate for the treatment of osteoporosis. For instance, Warner marketed a 35 mg delayed-release risedronate tablet, called ACTONEL®, which is the predecessor drug to the ATELVIA® drug at issue. Warner held patents covering risedronate and Warner's ACTONEL® product, which expired on December 10, 2013. Merck developed an alendronate product, marketed as FOSAMAX®; and Hoffmann-La Roche developed an ibandronate product, marketed as BONIVA®. (Joint Stipulation of Facts ¶¶ 42, 44, 57).

2. *The "Food Effect"*

Drugs that are administered by mouth travel from the mouth to the stomach, and then through the pylorus to the lower gastrointestinal tract—which includes the small and large

[4] Where available, the Court uses an exhibit's internal pagination.

intestine. (Joint Stipulation of Facts ¶¶ 88, 89). Bisphosphonate absorption occurs, to the largest extent, in the small intestine. (PTX 135, at 179). The small intestine consists of the duodenum, jejunum, and ileum. (DTX 234, at 589; Tr. 1A.106:3-6). There, the bisphosphonate passes from the intestines into the bloodstream.

There are two routes of transportation for molecules to pass from the intestine into the bloodstream: passing through the intestinal membrane cells themselves or passing through the spaces between the cells, called the tight junctions. (PTX 90, at 1744; Tr. 1A.107:1-8). Bisphosphonates do not pass through the membrane cells. Instead, they travel between the cells, through the tight junctions. (DTX 273, at 231; PTX 135, at 178-79; Tr. 1A.107:9-18). Once in the bloodstream, the bisphosphonate circulates; some is excreted and some is delivered to the bones, the site of the drug's action. (DTX 208, at 289; Tr. 1A.107:14-18).

Bisphosphonates are not absorbed, and do not pass into the bloodstream, when taken with a meal. This class of drug not only binds to the calcium in bone, it also binds to any stray calcium ions and other metals[5] it encounters in the stomach and intestines after a meal. (PTX 135, at 178; PTX 90, at 1745; Tr. 1A.108:23-109:4). In the gastrointestinal tract, calcium captures bisphosphonate, forming a combined calcium-bisphosphonate complex that is insoluble and is too big to pass through the intestinal tight junctions and into the bloodstream. (DTX 167, at 280, 283). Thus, when an osteoporosis patient simultaneously eats and takes her

[5] Divalent cations, including calcium, magnesium, and iron, interfere with bisphosphonate absorption. (Tr. 1A.109:10-16). The Court uses the term "calcium" in a general sense to refer to this group of metals.

bisphosphonate, she does not receive the benefit of the medicine because it never reaches the bone. (Tr. 1A.110:21-111:1). This phenomenon is known as the "food effect."

Because bisphosphonates interact with food, Warner's predecessor drug ACTONEL® had to be taken when the patient had fasted, specifically, after an overnight fast and at least 30 minutes before eating or drinking. (Joint Stipulation of Facts ¶ 53).

3. *Chelating Agents*

The compound disodium EDTA[6] binds to calcium and other divalent cations. This process is called chelation and EDTA is one of the most widely used and strongest chelators of calcium. (Tr. 1A.117:1-8). It tightly sequesters divalent ions, after which the ions cannot interact with other molecules. (Tr. 2A.26:9-27:5).

The bisphosphonate literature had shown that administering EDTA with bisphosphonate increased bisphosphonate absorption. Two mechanisms account for the increase in absorption: (1) chelation, in that EDTA acted as a calcium blocker; and (2) permeability enhancement, in that EDTA directly increased the permeability of the intestines. (*See* DTX 167, at 283; PTX 90, at 1745).

The first mechanism, calcium chelation, operates by blocking calcium from capturing the bisphosphonate active ingredient via competitive inhibition. (*See* DTX 167, at 283; PTX 90, at 1745). The active ingredient and the chelating agent both compete for the same pool of stray calcium. By introducing enough chelating agent, stray calcium is more likely to capture the

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[6] There are different types of EDTA with different properties. Unless otherwise noted in this opinion, the Court uses "EDTA" to refer to disodium EDTA. Likewise, there are different versions of risedronate. The Court uses "risedronate" to refer to risedronate sodium.

chelating agent than the active ingredient. (Tr. 2B.40:1-2). Like a decoy, chelating agents block calcium ions from capturing the bisphosphonate, while the bisphosphonate remains free to enter the bloodstream without interference.

The second mechanism, increasing intestinal permeability, works by widening the pathway between the tight junctions of intestinal cells—by which bisphosphonate travels from the intestine into the bloodstream—permitting more bisphosphonate to be absorbed. (DTX 273, at 232; DTX 167, at 283; PTX 90, at 1745). The tight junctions between cells have molecules of calcium embedded in the channels. EDTA binds to these molecules, making the spaces between cells wider, and increasing permeability for many particles. (DTX 167, at 283). Thus, larger molecules like bisphosphonates pass more easily into the bloodstream. (PTX 90, at 1745; PTX 135, at 179). But spreading the tight junctions creates a risk that bacterial fragments and increased levels of coadministered drugs will pass through these wider pathways to the bloodstream. (PTX 175, at 1249). Consequently, unduly spreading the tight junctions was viewed as undesirable. (DTX 167, at 280; PTX 90, at 1745; PTX 135, at 185).

c. The Challenged Patents

Both the ’459 and ’460 patents share a provisional application filed on May 24, 2004. The utility application that issued as the ’459 patent was filed on April 15, 2005. The utility application that issued as the ’460 patent was filed on November 23, 2005 and is a continuation-in-part of the application that issued as the ’459 patent. The ’459 patent, entitled “Dosage Forms of Bisphosphonates,” and the ’460 patent, entitled “Dosage Forms of Risedronate,” both issued on January 12, 2010. The patentee disclaimed the terminal part of the ’460 patent beyond the

expiration of the '459 patent, and both are scheduled to expire on January 9, 2028. (Joint Stipulation of Facts ¶¶ 34, 38). The inventors are listed as Richard Dansereau and David Burgio.

Claim 16 of the '459 patent, like claim 20 of the '460 patent, comprises one independent claim and several additional dependent claims. Claim 16 of the '459 patent is reproduced below:

> **8**. An oral dosage form having pharmaceutically effective absorption comprising:
>
> (a) from about 1 mg to about 500 mg of risedronate sodium;
>
> (b) from about 75 mg to about 250 mg of disodium EDTA; and
>
> (c) an enteric coating which provides for release of the risedronate sodium and the disodium EDTA in the lower gastrointestinal tract of a mammal.
>
> **13**. The oral dosage form of claim **8** comprising from about 10 mg to about 50 mg of risedronate sodium.
>
> **14**. The oral dosage form of claim **13** comprising about 100 mg of the disodium EDTA.
>
> **15**. The oral dosage form of claim **14** comprising about 35 mg of risedronate sodium.
>
> **16**. The oral dosage form of claim **15** wherein the enteric coating is a methacrylic acid copolymer.

(DTX 2, '459 patent, col. 38, ll. 50-57, col. 39, ll. 5-13). Claim 20 of the '460 patent is reproduced below:

8. An oral dosage form having pharmaceutically effective absorption comprising:

(a) from about 1 mg to about 250 mg risedronate sodium;

(b) from about 25 mg to about 500 mg of disodium EDTA; and

(c) an enteric coating which provides for immediate release of the risedronate sodium and the disodium EDTA in the small intestine of a mammal.

15. The oral dosage form of claim **8** comprising from about 15 mg to about 55 mg of the risedronate sodium.

16. The oral dosage form of claim **15** comprising from about 75 mg to about 250 mg of the disodium EDTA.

17. The oral dosage form of claim **16** comprising about 35 mg of the risedronate sodium.

19. The oral dosage form of claim **17** comprising about 100 mg of the disodium EDTA.

20. The oral dosage form of claim **19** wherein the enteric coating is a methacrylic acid copolymer.

(DTX 3, '460 patent, col. 24, ll. 47-55, col. 25, ll. 8-20).

As shown above, claim 16 of the '459 patent and claim 20 of the '460 patent are both limited to an oral dosage form with 35 mg of risedronate sodium, 100 mg of disodium EDTA, and a methacrylic acid copolymer enteric coating. Claim 16 of the '459 patent differs from claim 20 of the '460 patent in the location of release of the formulation: claim 16 requires "release . . . in the lower gastrointestinal tract," whereas claim 20 requires "release . . . in the small intestine." The small intestine is part of the lower gastrointestinal tract. (Joint Stipulation of Fact ¶ 89). Claim 20 of the '460 patent also adds the limitation "immediate release," which means "dissolution of the core tablet in less than 60 minutes, when measured by standard USP definitions." (DTX 3, '460 patent, col. 4, ll. 13-16).

One feature of the claimed invention is the addition of the limitation in both claims called "pharmaceutically effective absorption," which is defined in both the '459 and '460 patents as:

> an amount of a chelating compound high enough to significantly bind the metal ions and minerals in food but low enough not to significantly alter absorption of the bisphosphonate[7] as compared to absorption in the fasted state. That is, absorption is similar with or without food. Given the high variability of bisphosphonate absorption, fed exposure within about 50% of fasting exposure is expected to be "pharmaceutically effective absorption."
>
> (DTX 2, '459 patent, col. 4, ll. 59-67; DTX 3, '460 patent, col. 4, ll. 64-col. 5, ll. 5).

The patent applications that issued as the '459 and '460 patents originally did not contain the term "pharmaceutically effective absorption." (PTX 3, at 1138). After the PTO examiner rejected the claims as unpatentable—because earlier references disclosed bisphosphonates combined with EDTA to increase absorption—the patentee amended every claim to add the limitation "pharmaceutically effective absorption." (PTX 3, at 636-38, 1138; PTX 5, at 542-544, 648). The examiner allowed the claims after that amendment. The concept is to permit the patient to take the drug either with or without food; however, FDA has approved ATELVIA® only to be taken with food.

IV. THE TRIAL

At trial, the evidence centered upon whether the asserted claims of the '459 and '460 patents are invalid due to anticipation or obviousness.

a. Anticipation

"A patent is invalid for anticipation under 35 U.S.C. § 102 if a single prior art reference discloses each and every limitation of the claimed invention." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014). In order to anticipate, the prior art reference must contain "each

[7] In the '460 patent, this word, "bisphosphonate," is replaced with the word "risedronate."

of the limitations of the claim." *Scaltech, Inc. v. Retec/Tetra, LLC*, 178 F.3d 1378, 1383 (Fed. Cir. 1999). "Claimed subject matter is 'anticipated' when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). "[T]he dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010) (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991)) (internal quotations and alterations omitted). "[T]he party asserting invalidity due to anticipation must prove anticipation, a question of fact, by clear and convincing evidence." *Orion IP, LLC v. Hyundai Motor Am.*, 605 F.3d 967, 975 (Fed. Cir. 2010).

"[A] single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014). "[I]nherency operates to anticipate entire inventions as well as single limitations within an invention." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). Recognition of an inherent limitation in the prior art by a person of ordinary skill in the art is not required to establish inherent anticipation. *Id.* at 1377. An inherent limitation is one that is necessarily present and not one that may be established by "probabilities or possibilities." *See Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991). That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.*

1. The Brazilian Application

Teva introduced evidence that Brazilian Patent Application, No. BR2001-06601 (DTX 205), anticipated the claimed invention. The *Brazilian Application* was published on September 9, 2003. No patent has issued. It is prior art under 35 U.S.C. § 103(a) and (b) for both the '459 and the '460 patents. (Joint Stipulation of Facts ¶ 90). The *Brazilian Application* claimed: "at least one core containing one or more bisphosphonates, at least one core or core coating containing a chelating agent, said core or cores being coated individually or together by a gastroresistant and enterosoluble layer." (DTX 205, at 9). With respect to bisphosphonates, the *Brazilian Application* lists risedronate as well as thirteen additional bisphosphonates and their pharmaceutically acceptable salts and hydrates. (*Id.* at 5-6). Regarding chelating agents, it lists four acceptable chelating agents, including EDTA in either monosodium or disodium form. (*Id.* at 5). Finally, it disclosed a "gastroresistant and enterosoluble coating" to deliver the chelating agent "only into the small intestine," (*id.* at 3); the application requires bypassing the stomach so that there is no loss of chelating agent in the stomach, (*id.* at 4). Acceptable coatings include "copolymers of methyl methacrylate – methacrylic acid." (*Id.* at 6). The coating "preferably dissolve[s] rapidly in a neutral environment." (*Id.*). The bisphosphonate, chelating agent, and delayed release mechanism are combined to "increase[] the absorption of bisphosphonates by the action of chelating agents" using two mechanisms: "a) reduction of the formation/solubilization of insoluble complexes of bivalent [calcium and magnesium] ions with bisphosphonates, and b) increase in permeability of the intestinal mucosa." (*Id.* at 3).

The parties agree that "somewhere in [the *Brazilian Application*] are all of the elements of the asserted claim" except "pharmaceutically effective absorption," (Tr. 4A.51:16-23). They

dispute whether the *Brazilian Application* disclosed the particular claimed amount of 35 mg risedronate sodium combined with the particular claimed amount of 100 mg disodium EDTA.

2. *Amount of Risedronate Disclosed*

As in the asserted claims, the *Brazilian Application* used a subset of bisphosphonates for the purpose of "inhibiting osteoclast-mediated bone resorption." (DTX 205, at 2). The *Brazilian Application* did not instruct the use of a particular amount of risedronate sodium. Rather, it called for an "effective quantity" of any bisphosphonate, including risedronate sodium, where the "intervals (for example, daily or weekly) . . . , the effective quantity, and the rate of release depending on the pathology to be treated, as known to a person skilled in the art."

It is undisputed that risedronate sodium was "well-known as of 2005 . . . [as a] commercially available salt of risedronate." (Tr. 1A.126:4-7). Defendant's formulation scientist Dr. John Yates—the executive director of clinical research at Merck during development of FOSAMAX®—testified that a person of ordinary skill at the relevant time would understand the term "effective quantity" of risedronate to be a 35 mg once-weekly dose of risedronate sodium. (Tr. 1A.126:21-25). The 2002 ACTONEL® label listed the only approved doses of risedronate as the 35 mg weekly dose of risedronate sodium for osteoporosis, the 5 mg daily dose for osteoporosis, and the 30 mg formulation of risedronate sodium for Paget's disease. (DTX 185, at 5; Tr. 1B.26:4-9). The 35 mg once-weekly dose was the most commonly prescribed regimen of risedronate for osteoporosis. (Tr. 1B.25:23-25).

On the other hand, Dr. Stanley Davis—a professor of pharmaceutical science—testified that the *Brazilian Application* disclosed the use of substantially less than 35 mg risedronate based on the specification's statement that, "with this invention we obtain an effective treatment with a

small quantity of bisphosphonate compared to the current treatment." (DTX 205, at 4). Although it acknowledged that small quantities may be useful, the *Brazilian Application* explicitly suggested selecting an "effective quantity" of any bisphosphonate as "known to a person skilled in the art," which would include the 5 mg daily and 35 mg weekly dose. Unlike the amount of EDTA, for which it recommended "lower than the known quantities," the *Brazilian Application* did not suggest using less than the known "effective quantity" of the bisphosphonate. Consequently, a person of ordinary skill in the art would read the *Brazilian Application* to disclose as an acceptable choice for a bisphosphonate a weekly dose of 35 mg risedronate sodium.

3. Amount of EDTA Disclosed

It is undisputed that the *Brazilian Application* did not disclose solely 100 mg EDTA for use in a formulation. Rather, it disclosed a ten-fold range of EDTA to be paired with a bisphosphonate based on relative molarity. (Tr. 1A.128:18-24). Dr. Yates opined that the reference taught a person of skill in the art using risedronate to choose between 20 mg and 175 mg disodium EDTA.[8] (Tr. 1A.128:18-24). The claimed amount, 100 mg disodium EDTA, is within the *Brazilian Application's* disclosed preferred range for disodium EDTA.

"[I]f the prior art . . . discloses only a range of values, and the new claim recites an overlapping but different range, we have said that the prior-art reference must describe the

[8] Dr. Yates calculated this range based on the *Brazilian Application's* preferred upper limit for EDTA, that it is "preferable but not exclusively preferable for the daily intake of chelating agent, particularly EDTA, not to exceed about 175 mg"; and its preferred lower limit, that the agent should be "greater than 10% mol/mol [as compared to the bisphosphonate], particularly higher than 50% mol/mol." (DTX 205, at 6). He testified that, for a 35 mg risedronate dose, the preferred lower limit was about 20 mg EDTA. (Tr. 1A.128:18-24). This calculation was not disputed.

claimed range with sufficient specificity to anticipate the limitation of the claim—a broad prior-art disclosure that encompasses a narrower claimed range is sometimes not enough for anticipation." *In re Haase*, 542 F. App'x 962, 965-66 (Fed. Cir. 2013) (internal quotation marks and alterations omitted). Particularly where there is "considerable difference between the claimed . . . range and the range in the prior art," there is no anticipation. But a prior art range anticipates a claimed value if "a trial . . . reveal[s] a minimal difference between the [prior art] range . . . and the [claimed value], or that one of ordinary skill would interpret [the prior art range] as clearly disclosing [the claimed value] as an acceptable choice within that range . . . ." *OSRAM Sylvania, Inc. v. Am. Induction Tech.*, 701 F.3d 698, 706 (Fed. Cir. 2012). Evidence that the claimed value is not "critical" or that "the claimed method [does not] work[] differently at different points within the prior art range" indicates that a person of ordinary skill would have envisioned that the claimed value was an acceptable choice within the prior art. *See ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012) (finding prior art variable range of "150 ppm or less" anticipated claimed value of 50 ppm where there was no "evidence that different portions of the broad range would work differently [and] no allegation of criticality or any evidence demonstrating any difference across the range.").

It is uncontested that, for the bisphosphonate-EDTA formulation to work effectively, the amount of EDTA must be within a certain range: too low a dose of EDTA is insufficient to block calcium from capturing the active ingredient in the fed state, resulting in negligible absorption; too much EDTA will unduly spread the tight junctions in the fasted state, resulting in too much absorption and other undesirable effects. The question is whether the patentee's selection of a 100 mg EDTA dose from the *Brazilian Application's* disclosed range of 20 to 175 mg EDTA was critical to the invention's effectiveness. Formulation scientist Dr. Yates testified about

literature that taught that substantially all of the calcium in a calcium-rich meal would be competitively chelated by 75 to 150 mg EDTA in the small intestine, (Tr. 1B.60:21-61:4; Tr. 1B.62:14-17; *see also* Tr. 4B.24:16-23). Both Dr. Yates and Dr. John Dillberger—a former director of toxicology at several pharmaceutical companies—opined that far more than 175 mg EDTA would be required to increase absorption via altering the tight junctions in the fasted state. (Tr. 2A.49:3-12; Tr. 4B.89:18-90:13). Consequently, these experts' reasoning supports an inference that, at the very least, between 75 and 175 mg of disodium EDTA will work effectively.

On the other hand, the patentee Burgio testified that the invention required more precision than simply choosing a dose from the prior art range. He opined that success required balancing interdependent variables such that a formulation would not work unless "the doses of both bisphosphonate and the chelator . . . [were] titrated just properly." (Tr. 4A.72:11-14). He claimed that the particular dose of EDTA must vary with: the amount of the bisphosphonate; the type of bisphosphonate; and the location of release.

The weight of the evidence at trial, however, established otherwise; to wit, that the proportion of bisphosphonate to EDTA does not affect absorption because the two ingredients work independently of each other and are not interdependent. Defendant's formulation scientist Dr. Yates, Plaintiffs' toxicologist Dr. Joseph Rodricks—a former FDA Deputy Associate Commissioner—and Defendant's toxicologist Dr. Dillberger all agreed that an increase in the bisphosphonate dose does not require a corresponding increase or decrease in EDTA. (*See* Tr. 2B.41:8-20 ("THE COURT: So the amount of EDTA is not necessarily dependent in any way or connected to the amount of risedronate . . . it works independently? DR. DILLBERGER:

Independent. DR. RODRICKS: Independent. THE COURT: And I see both sides nodding yes to that.")).

The challenged patents confirm this reasoning. The specification asserts that a formulation will be pharmaceutically effective if: (1) a "weekly oral dosage form contains from about 10 to about 50 mg risedronate," (DTX 2,'459 patent, col. 7, ll. 21-23); (2) "[w]hen the chelating agent is disodium EDTA, the preferred range is from about 55 mg to about 500 mg, preferably from about 75 mg to about 250 mg per unit dose," (DTX 2,'460 patent, col. 9, ll. 37-41); and (3) it is delivered to the "lower gastrointestinal tract."[9] The patents encompass a number of "examples [that] illustrate the formulations . . . of the present invention," (DTX 2, '459 patent, col. 19, ll. 18-19), which include embodiments with double the amount of risedronate as EDTA, (DTX 2, at Example II, '459 patent col. 20, ll. 35-65 (150 mg risedronate sodium and 75 mg disodium EDTA)); far less risedronate than EDTA, (*id*., at Example IV, col. 22, ll. 60-65 (5 mg risedronate sodium and 75 mg disodium EDTA)); and levels of EDTA that vary independently of risedronate, (*id.*, at Example VIII, col. 27, ll. 55-65 (35 mg risedronate sodium and 150 mg disodium EDTA)). Despite the fact that the ratio of EDTA to bisphosphonate varies greatly, all embodiments are stated in the specification as exhibiting "pharmaceutically effective absorption."

Nor did the evidence at trial indicate that a particular level of EDTA was necessary for a particular type of bisphosphonate. Again, every testifying toxicologist agreed that combining bisphosphonates and chelating agents was "not like a recipe between the two. Because they're

[9] The '460 patent states a similar preference for between 15 and 55 mg risedronate, col. 6, ll. 22-25, for between 75 and 250 mg disodium EDTA, col. 8, ll. 14-17, and with release in the "small intestine."

not interacting with each other." (Tr. 2B.39:1-41:25). Even Plaintiffs' formulation scientist, Dr. Davis, knew of no evidence that bisphosphonates and EDTA were interdependent. (Tr. 4A.45:7-47:2). The record evidence is clear that EDTA does not interact with the bisphosphonate at the relevant doses. Its role is separate: to block calcium ions in food from capturing the active ingredient. (Tr. 2B.39:1-40:25).

Moreover, the '459 and '460 patents encompass pharmaceutically effective formulations containing a range of 75 mg to 250 mg disodium EDTA, but every claimed formulation requires "risedronate sodium" and not any other bisphosphonate. Thus, the patents assert that the disclosed range of 75 mg to 250 mg EDTA will work effectively with risedronate sodium. It does not indicate that any particular level of EDTA is critical for each type of bisphosphonate.

Similarly, the '460 patent asserts that EDTA between 75 mg and 250 mg will produce "pharmaceutically effective absorption." Every claim of that patent requires release in the "small intestine." Thus, a range of EDTA is intended to be effective in the small intestine, rather than any particular level of EDTA.

The evidence at trial, including the expert testimony and the patents' specification, revealed that a wide range of EDTA between 75 and 175 mg will allow the formulation to work as claimed. The formulation does not require specifically calculating the level of EDTA based on the type of bisphosphonate, amount of bisphosphonate, or location of release within the small intestine. Nor was evidence introduced showing that levels lower than 75 mg EDTA would be ineffective.[10] In sum, the evidence showed that the claimed amount of 100 mg was not critical

[10] Although some significantly lower doses were tested by Teva and did not achieve "pharmaceutically effective absorption," the record is silent as to the reason these formulations did not meet the limitation.

compared to the prior art's disclosure of between 20 and 175 mg EDTA. The clear and convincing evidence at trial "reveal[ed] a minimal difference between the [prior art] range . . . and the [claimed value]." *OSRAM*, 701 F.3d at 706. "[O]ne of ordinary skill would interpret [prior art range] as clearly disclosing [the claimed value] as an acceptable choice within that range . . . ." *Id.*

4. Whether a List of Ingredients Anticipates a Combination

The *Brazilian Application* disclosed the combination of one of approximately fourteen bisphosphonates (or their salts), with one of about four chelating agents (or their salts), and one of about six delayed-release mechanisms. Included in the *Brazilian Application's* disclosure were the claimed ingredients, including "risedronate . . . and the pharmaceutically acceptable salts and hydrates thereof"; used in combination with a subset of chelating agents, including "EDTA . . . in monosodium or disodium form"; and a delayed release mechanism, including "copolymers of methyl methacrylate – methacrylic acid."

When prior art discloses a list of acceptable ingredients combined with another list of acceptable ingredients for a particular purpose, "[t]he question for purposes of anticipation is therefore whether the number of categories and components in [the prior art] was so large that the combination . . . would not be immediately apparent to one of ordinary skill in the art." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1362 (Fed. Cir. 2012). If the amount of combinations of explicitly named ingredients is a "defined and limited class" and the amounts of the ingredients are within the prior art range, the result will be anticipated. *Id.* at 1361-62; *see also Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005)

("[S]pecific disclosure, even in a list, makes this case different from cases involving disclosure of a broad genus without reference to the potentially anticipating species.").

The prior art *Brazilian Application* disclosed a specific and limited number of bisphosphonates by name combined with a specific and limited number of chelating agents and delayed release mechanisms. The particular ingredients and amounts claimed by Plaintiffs were identified as acceptable within the prior art's disclosed categories and ranges. The number of possible combinations in the *Brazilian Application* was not "so large that the combination . . . would not be immediately apparent to one of ordinary skill in the art." Nor was evidence adduced that other combinations disclosed would not have been successful for the claimed purpose.

The *Brazilian Application* disclosed the claimed elements in the same combination, for substantially the same function: an active ingredient to prevent osteoporosis; a chelating agent to chelate calcium ions in the small intestine, and a delayed release mechanism to bypass the stomach. Thus, it does not require combining different disclosures or random selection from unrelated elements in the prior art, rather it "combine[s] [the elements] in the same way as recited in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).

5. *Whether "Pharmaceutically Effective Absorption" is Disclosed*

The *Brazilian Application* did not use the term "pharmaceutically effective absorption." Distinguishing the prior art to overcome the Patent Office's initial rejection of the patents, the patentee stated that "pharmaceutically effective absorption" requires EDTA be used only to "address the food effect" via chelation, not to increase intestinal permeability because increased permeability would "result in vastly different bisphosphonate absorption and therefore exposure

depending on whether the patient is in the fasted state . . . or fed state." (PTX 3, at 1151). Thus, the definition of "pharmaceutically effective absorption" requires: (1) choosing an amount of EDTA sufficient to "significantly bind the metal ions and minerals in food" after a meal; (2) but which is "low enough not to significantly alter absorption" by increasing intestinal permeability; (3) with the result that "absorption is similar with or without food . . . [F]ed exposure within about 50% of fasting exposure is expected to be 'pharmaceutically effective absorption.'"

A. "Significantly Bind the Metal Ions in Food"

The concept of using sufficient EDTA to bind to the metal ions in food is found within the *Brazilian Application.* It instructed that delivering the formulation of bisphosphonate and chelating agent to the small intestine "eliminate[s] the interaction of [bisphosphonate] with the contents of the stomach," including the calcium and magnesium ions found in food that bind to bisphosphonate and prohibit the drug from entering the bloodstream. (DTX 205, at 3). The *Brazilian Application* proposed a solution to reduce the interaction of bisphosphonate with calcium and magnesium ions: using a chelating agent to "capture[] the bivalent ions in preference to the bisphosphonate, permitting the bisphosphonate to remain free for absorption by the body." (*Id.* at 4). Both parties' experts agreed that a person of ordinary skill in the art would have understood that the chelation mechanism disclosed in the *Brazilian Application* was intended to significantly bind metal ions from food in the small intestine so that the bisphosphonate remains free to be absorbed. (Tr. 1A.129:3-17 (Dr. Yates); Tr. 1A.133:9-11; Tr. 4B.87:22-25 (Plaintiffs' formulation scientist Dr. Davis stating that "the first part of [the *Brazilian Application*] is to avoid the interaction of the bisphosphonate with calcium and magnesium. And that would be something say in -- well, in the fed state.")). Although the *Brazilian Application* did not explicitly discuss the food effect, the clear purpose of the chelation

mechanism is to neutralize the metal ions in food that result in decreased absorption of bisphosphonate in the fed state. (Tr. 4B.86:4-25).

B. "Low Enough not to Significantly Alter Absorption"

The *Brazilian Application* did not teach this limitation, rather it suggests using EDTA to "increase permeability of the intestinal mucosa." Although the reference intended to alter absorption, some evidence at trial indicated that the *Brazilian Application's* preferred upper limit for disodium EDTA of 175 mg was, in fact, insufficient to alter intestinal permeability, and that the disclosed range was inherently low enough not to "significantly alter absorption."

EDTA alters absorption of bisphosphonate when there is sufficient unchelated EDTA to bind to the ions in the tight junctions, widening the pathways between cells. This does not occur when there is sufficient dietary calcium, as in the fed state. (Tr. 2B.68:25-69:3; Tr. 2B.63:18-22). Even in the fasted state, there is a calcium buffer which protects the cell walls from unchelated EDTA. (Tr. 2A.59:13-19). But where the amount of disodium EDTA exceeds both dietary calcium and the cellular calcium buffer, EDTA will harmfully alter intestinal permeability. Dr. Yates and Dr. Dillberger both opined that far more than 175 mg of disodium EDTA on an empty stomach would be required before there would be a substantial increase in intestinal permeability or increase in absorption. (Tr. 2A.49:3-12; Tr. 4B.89:18-90:13). Although Dr. Rodricks contested whether a person of ordinary skill would have known so at the time, he did not dispute that 175 mg would be insufficient to modify the tight junctions. Thus, all of the record evidence indicates that amounts of disodium EDTA less than 175 mg do not substantially alter absorption by increasing intestinal permeability.

C. "Similar Absorption"

As stated above, a skilled artisan using a formulation containing 35 mg risedronate and between 75 and 175 mg EDTA would not significantly alter absorption but would significantly bind to the metal ions in food. However, it is undisputed that even the claimed amount of 35 mg risedronate and 100 mg EDTA does not always produce "similar absorption" in the fed and fasted state. After the patents were filed, Plaintiffs discovered that they could achieve "similar absorption" using the claimed formulation in the small intestine, but not in the ascending colon. (PTX 352, at s3). Although some of the disclosed embodiments in the *Brazilian Application may* result in similar absorption in the fed and fasted state, there is insufficient evidence to clearly and convincingly find that any embodiment would *necessarily* produce the claimed element. *See Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991). Thus, while it is a close question, the evidence does not reach the clear and convincing level that one practicing any disclosed embodiment of the *Brazilian Application* would inherently produce the claimed element of "pharmaceutically effective absorption." If the burden of persuasion were different, the outcome might well be different. Here, the *Brazilian Application* did not anticipate the asserted claims. *See Allergan*, 754 F.3d at 960-61.

b. Obviousness[11]

"A patent may not issue 'if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

[11] Although 35 U.S.C. § 103 was modified by the Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 6 (2011), the Court applies the pre-AIA statute because the patentee filed its application before the effective date of the amendments. *Q.I. Press Controls, B.V. v. Lee*, 752 F.3d 1371, 1377 n.3 (Fed. Cir. 2014).

the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068 (Fed. Cir. 2012) (quoting 35 U.S.C. § 103(a)).

Obviousness is a question of law based on underlying factual findings regarding: the scope and content of the prior art; the differences between the claims and the prior art; the level of ordinary skill in the art; and objective considerations of nonobviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966)); *see also Cyclobenzaprine*, 676 F.3d at 1068. Obviousness is analyzed from the viewpoint of a person of ordinary skill in the art, who has "ordinary creativity." *See KSR*, 550 U.S. at 421. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418. "A court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

1. *Level of Ordinary Skill in the Art as of April 2005*[12]

The parties agree that the level of ordinary skill in the art is an individual with a Ph.D. or M.D. in pharmaceutical sciences with substantial practical experience developing and testing pharmaceutical formulations in humans, and who has access to other professionals in the formulation sciences, gastroenterology, and the treatment of osteoporosis.[13] (Tr. 1A.122:7-14). The Court agrees with and adopts this level of skill in the art and the concomitant description of a skilled artisan.

2. *Scope And Content of the Prior Art*

A. Skilled Artisan's Knowledge of the Bisphosphonate Food Effect Problem

It was well-known by the April 2005 effective filing date of the challenged patents that bisphosphonate absorption decreased when taken with a meal because of its interaction with the calcium in food. (Tr. 1A.109:8-16; PTX 90, at 1743, Table 2 (1994 publication on oral absorption of bisphosphonates showing about a five-fold decrease when administered with food as compared to the fasted state); PTX 135, at 178 (2000 publication stating that "oral absorption of [bisphosphonates] is diminished when the drug is given with meals, especially in the presence of calcium and iron."); DTX 185, at 17). For this reason, patients taking any member of the class of bisphosphonates were instructed to fast overnight before administration, and to wait 30 minutes after administration before eating breakfast. (Tr. 1A.112:21-113:2; Joint Stipulation of Facts ¶¶ 48, 50 (FOSAMAX® 2000); ¶¶ 57, 61 (BONIVA® 2003)).

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[12] The parties have stipulated that the effective filing date of the invention is no earlier than April 15, 2005. (Joint Stipulation of Fact ¶ 81).

[13] The parties agreed that there were no "meaningful" differences between their positions on this issue. (Tr. 1A.61:14-62:9).

Some patients found these dosing instructions inconvenient. (Tr. 1A.113:3-15). Other patients did not follow the dosing instructions and, as a result, did not receive an effective dose. (PTX 118, at 491, Figure 2 (1998 comparative research study finding that over 50% of patients administered bisphosphonate incorrectly and in a manner that reduced absorption)). As one inventor testified, "[i]t was well understood . . . in the industry . . . that indeed this was a problem." (Tr. 4A.70:24-25).

A skilled artisan[14] would have understood the cause of the food effect. Well before 2005, it was known that "cations [like calcium] will interfere with the absorption of ACTONEL." (DTX 185, at 17; DTX 208, at 295 (1995 publication stating that "the bioavailability of bisphosphonates is low, presumably a result of their highly charged structure and their tendency to form insoluble salts with polyvalent cations."); DTX 167, at 280, 283). As Warner Chilcott acknowledged, by 2004, "the current science told us" that the food effect was caused by "divalent cations in food, such as calcium, . . . bind[ing] to risedronate in the GI tract making the complex unavailable for absorption." (Tr. 2B.121:2-10 (Warner's Fed. R. Civ. P. 30(b)(6) designee Dr. Gary Galletta); Tr. 4A.69:20-23). It was also known that reducing calcium-bisphosphonate interaction was necessary to solve the problem. (Tr. 1B.124:22-25 (patentee Richard Dansereau stating he was interested in calcium concentrations because "it was a known fact that chemically risedronate does chelate calcium"); DTX 185, at 16 (predecessor drug ACTONEL® label prohibiting patients taking calcium supplements with their dose)).[15] Moreover,

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[14] The Court uses the term "skilled artisan" as interchangeable with "a person of ordinary skill in the art as of April 2005."

[15] Before trial, Warner argued that the causes of "the food effect are complex and, as of 2005, were poorly understood." But at trial Plaintiffs did not present evidence to support this

the magnitude of the problem was understood: the 1992 *Mahé Reference* measured the particular concentration of calcium within different locations in the gastrointestinal tract after a meal. (DTX 133, at 413 (comparing ions of calcium and magnesium in the ileum versus the jejunum after a meal)).[16]

The Court finds that, at the time the challenged patents were filed, a person of ordinary skill in the art would have recognized: (1) the problem—that bisphosphonates were ineffective when taken with food; (2) the cause and magnitude of the problem—that a particular amount of calcium from a meal captured the active ingredient risedronate and prevented it from being absorbed; and (3) the goal—to defeat the food effect by reducing the formation of calcium-risedronate complexes.

The skilled artisan would have known of one solution—the use of a calcium chelator to block calcium ions from forming calcium-bisphosphonate complexes—because that solution had been well explored in the literature.

B. EDTA's Use as a Chelator of Calcium

Long before 2005, many studies had shown how EDTA operated to increase bisphosphonate absorption. The 1991 Janner study (DTX 167, at 283) tested an oral formulation

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argument. Nor did they preserve the factual issue in their final proposed findings of facts. "This court need not reach issues [Plaintiffs] did not raise properly in proposed post-trial findings." *In re Omeprazole Patent Litig*., 483 F.3d 1364, 1375 (Fed. Cir. 2007).

[16] Risedronate is absorbed over a 30 minute period. The bisphosphonate literature taught that risedronate could be released anywhere along the lower gastrointestinal tract without statistically significant differences in the rate or extent of absorption. (DTX 273, at 230). Based on *Mahé*, a skilled artisan would expect the distal ileum to be exposed to about 0.3 millimolar concentration of calcium over a 30 minute period. (Tr. 1B.29:14-30:3).

containing a bisphosphonate and "a calcium chelator, EDTA," in rats and found increased intestinal absorption of the bisphosphonate. He noted that "bisphosphonates form polynuclear complexes with calcium [which] are precipitated as calcium-bisphosphonates" and posited that EDTA, as a chelation agent, would "reduce the formation of insoluble calcium-bisphosphonate and polynuclear complexes and hence, contribute to a better absorption of the bisphosphonates." (*Id.* at 280, 283). He also noted an alternative mechanism whereby EDTA bound to the calcium in the intercellular channels of the rat intestine, "directly enhancing intestinal permeability." *Id.* The 1994 Lin study expanded on the concept of the chelation property: "EDTA, by sequestration of calcium (or other metals), prevented the formation of a metal-alendronate complex which is poorly absorbed from the gastrointestinal tract." (DTX 168, at 1745). He also explained the permeability enhancing property: "chelating agents might alter the integrity of the intercellular tight junctions at high doses resulting in an increase in absorption" because "the tight junctions are formed by specific proteins and divalent cations, such as Ca^{2+} and Mg^{2+}." (*Id.*).

AstraZeneca's International Patent Publication WO 00/61111 connected EDTA's chelating properties as a possible solution to the "diminished [absorption] when [bisphosphonate is] given with meals, especially in the presence of calcium." (DTX 206, at col. 1, ll. 23-24). It suggested using chelating agents like EDTA, as well as various other agents, in combination with bisphosphonates to achieve "enhanced and/or less variable absorption [of] bisphosphonates," (*id.* at col. 4, ll. 4-7), and "allow the patient to take the medicament more conveniently, e.g. together with food intake," (*id.* at col. 2, ll. 15-18).

EDTA's use as a chelator of calcium was not limited to bisphosphonates. The 1978 *Poiger Reference* used disodium EDTA as a chelating agent to eliminate the food effect in humans observed with a drug called tetracycline. Like bisphosphonate, absorption of tetracycline

is greatly reduced in the presence of "the dietary content of metal ions" like calcium because "[t]etracycline forms chelates with calcium . . . which impairs permeation of the drug." (DTX 162, at 131). Using a formulation with an amount of EDTA that is "equivalent as a molar ratio to the amount of calcium" expected in the stomach, Poiger found that absorption of the active ingredient after ingesting calcium-rich milk was "almost equivalent" to absorption when the subjects had fasted. (DTX 162, at 129-30; *see also* Tr. 1B.11:2-12). Using this equimolar ratio, "the bioavailability of the drug remained constant irrespective of the diet." (DTX 162, at 131, Table 1 (experiment nos. 2 & 4 showing that tetracycline administered with EDTA showed fed absorption better than 50% of fasting absorption)). Moreover, disodium EDTA administered in the fasted state did not "significantly change absorption of the drug." (*Id.* at 129). In other words, even with 250 mg disodium EDTA, there was no enhanced absorption in the fasted state. (*Id.*, Table 1 (experiment nos. 1 & 2 showing no statistically significant increase in absorption of tetracycline administered in the fasted state without EDTA compared to tetracycline administered in the fasted state with EDTA)). This "obviate[d] special directions about diet during therapeutic use of [tetracycline]." A skilled artisan would recognize that Poiger disclosed a formula—an equimolar ratio of EDTA to expected calcium, (Tr. 1B.30:13-14)—for a formulation that would significantly bind to metal ions in food without significantly altering absorption, leading to similar bioavailability irrespective of diet.[17] (Tr. 1B.12:6-13:14).

[17] In their post-trial proposed fact findings, Plaintiffs assert that, unlike bisphosphonate, "Tetracycline absorption in the fasted state . . . is not enhanced by EDTA," therefore, "a POSA would not find [bisphosphonates] and tetracycline comparable in terms of absorption." (Pls.' Proposed Findings ¶ 57). Plaintiffs cite no testimony, expert or otherwise, to support this proposed finding of fact. Here, the strong weight of the factual evidence is to the contrary: "the mechanism by which bisphosphonate absorption is reduced with calcium is actually the same mechanism by which tetracycline absorption is reduced, which is the formation of insoluble calcium complexes." (Tr. 1B.13:11-14).

The Court also notes and restates its findings on the *Brazilian Application* above regarding the well-known use of EDTA as a calcium chelator to enhance bisphosphonate absorption. *See* § IV(a), *supra*. Additionally, both parties' experts agreed that a person of ordinary skill in the art would have understood that the calcium chelation mechanism disclosed in the *Brazilian Application* was intended to significantly bind metal ions from food in the small intestine after a meal so that the bisphosphonate remains free to be absorbed. (Tr. 1A.129:3-17 (Dr. Yates); Tr. 1A.133:9-11; Tr. 4B.87:22-25 (Davis)).

3. Objective Considerations

A. Teaching Away

Toxicology literature in the early 1990s indicated that the amount of EDTA required to be useful in the stomach was too high for safe administration to human patients. Before the *Brazilian Application* was published, the literature taught that the minimum effective oral dose of EDTA that enhanced absorption of bisphosphonate as a chelator of calcium was about 700 mg, scaled to human weight. (Tr. 1B.21:19-22). The literature, including Ezra, Lin, and Janner, also concluded that these high oral doses of EDTA were not clinically useful. (DTX 167, at 283; PTX 90, at 1745; PTX 135, at 185). However, in 2003 the *Brazilian Application* published and distinguished Lin and Janner's delivery to the *stomach* using "extremely high [doses] (more than 100 mg/kg of body weight)," from its proposed delivery "only into the *small intestine*" using "chelating agents in quantities lower than the known quantities." (DTX at 3, 6). This prior art proposed a limit of 175 mg EDTA. The *Brazilian Application* explained that delivery in the small intestine "eliminate[s] the interaction of these [chelating] agents with the contents of the stomach," where an abundance of calcium ions would otherwise "consume" the chelating agent

before it reaches the small intestine. (*Id.* at 3). "[R]elease of the chelating agents only into the small intestine permits a reduction in the dosage administered for the desired result, which is increased absorption of the bisphosphonates." (*Id.*).

Dr. Yates confirmed that a skilled artisan in 2005 would have known that delivery in the small intestine, rather than the stomach, would require far less chelating agent because the stomach has a higher concentration of calcium after a meal than the small intestine. (Tr. 1A.131:18-132:2). No expert witness testified to the contrary. Dr. Yates concluded that a skilled artisan would have known that 75 to 150 mg EDTA delivered to the small intestine would be sufficient to effectively chelate dietary calcium. (Tr. 1B.60:21-61:4).

"[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR Int'l, Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). "The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). "Where the prior art contains apparently conflicting teachings . . . each reference must be considered for its power to suggest solutions to an artisan of ordinary skill considering the degree to which one reference might accurately discredit another. . . [T]he

prior art must be considered *as a whole* for what it teaches. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165-66 (Fed. Cir. 2006) (internal alterations and quotation marks omitted).

Compared to the broad conclusions drawn by Lin and Janner based on delivery of very high doses of EDTA to the stomach, the *Brazilian Application* made specific distinctions between safe and unsafe levels of EDTA delivered to the small intestine.[18] A person of ordinary skill in the art in 2005 would have understood that significantly lower doses than those used by Janner would be useful for the claimed purpose. Placed in context, Lin and Janner teach only that EDTA "alter[s] the integrity of the intercellular tight junctions at high doses," (DTX 168, at 1743 (Lin)), and that doses higher than 700 mg EDTA are "unsuitable," (PTX 82, at 283 (Janner)). But the literature does not discourage the use of the far lower doses known to be effective in the small intestine. Nor does it suggest that 100 mg EDTA will be unproductive if released in a location other than the stomach, like the small intestine. Reading the literature as a whole, Lin and Janner do not teach away from the claimed amount of EDTA. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014); *see Medichem*, 437 F.3d at 1165-66 (finding that, where some references broadly suggested claimed compound would not work and others suggested it would work in low concentrations, prior art did not teach away).

Additionally, some of the literature noted the danger of using any amount of EDTA for certain purposes, while other references indicated that EDTA was generally safe. Attempting to

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[18] The Ezra publication, a literature review, quotes Janner and Lin for the proposition that EDTA's use in pharmaceuticals is "impossible." (PTX 135, at 185). It did not conduct additional research or explore administration in the small intestine rather than stomach. Taken together, these publications advise against using EDTA at doses above 700 mg in the stomach, but do not discredit—or even note—the more recent research on the delivery of lower doses of EDTA to the small intestine.

reconcile these seemingly contrary conclusions, the Court heard expert testimony from two toxicologists: Dr. Rodricks for the Plaintiffs and Dr. Dillberger for the Defendant. Both experts agreed that none of this research directly tested the safety of the claimed dose delivered in the claimed manner. Although they differed in their ultimate conclusion about whether a skilled artisan would have believed that the claimed amount of EDTA was safe, when the Court posed its own questions to them, they were largely in agreement about what the literature taught in 2005. They agreed that there would be little concern if a dose of EDTA were administered with sufficient food. (Tr. 2B.68:25-69:3). Even without dietary calcium—as in the fasted state—both experts agreed that a skilled artisan would have known that there would always be calcium ions in the digestive tract. (Tr. 2B.69:4-10; Tr. 2B.57:16-58:7; Tr. 2B.78:17-19).

Dr. Dillberger testified that this calcium buffer—in the intestinal cells, the fluid surrounding the cells, and the blood supply to those cells—protects cellular tight junctions from EDTA; it must be depleted before there would be a concern that the tight junctions would be damaged. (Tr. 2A.59:13-19). He opined that a person of ordinary skill as of 2005 would know that these reserves of cations were available for EDTA to chelate, (Tr. 2A.49:3-12), and that merely fasting for a day would not clear the intestinal tract of this reserve of calcium, (Tr. 2B.57:22-58:7). Dr. Rodricks did not dispute that residual calcium in the cells would act as a buffer to protect the tight junctions. (Tr. 2B.69:4-10). Both experts agreed that extremely high doses like 700 mg, 7,000 mg and 35,000 mg, scaled to human weight, depleted the calcium buffer and caused separation of the tight junctions, (Tr. 1B.21:19-22), and that very low doses like 5 mg were recognized as so safe in pharmaceutical products that they were listed in the

Inactive Ingredient Guide, indicating that FDA required no additional safety research for such levels.[19] (Tr. 2A.64:17-22; Tr. 2B.12:5-9; Tr. 2B.14:22-15:11).

The factual dispute between the toxicologists was narrowed to whether a skilled artisan would have been deterred from delivering 100 mg disodium EDTA to the small intestine because of a concern that it would deplete the calcium buffer in the fasted state and harm the small intestines. The available literature was only tangentially related to this inquiry.

Before turning to this inquiry, the Court addresses the proffered references. The World Health Organization's Joint Expert Committee on Food Additives reported that 2.5 mg/kg per day of disodium EDTA was safe, (DTX 95, at 35); and disodium EDTA had achieved Generally Regarded as Safe ("GRAS") status, (DTX 134; Tr. 1B.129:17-20; DTX 87, at 3-4). But this safe daily-intake level assumed that EDTA was administered with food containing calcium. There was little safety concern when EDTA is administered with sufficient food or calcium. (Tr. 2B.68:25-69:3 (Dr. Rodricks)). Thus, the food additive literature does not bear in a persuasive way on the issue of potential concern.

Similarly, certain literature claimed that EDTA had "damaging effects on mucosal integrity," (PTX 74, at 427-28 (Van Hoogdalem)); was impractical because it has "been shown to be harmful to the epithelial cells of the intestine," (PTX 80, at 2 (Muranishi)); and that "EDTA in any kind of clinical study on humans would be inappropriate." (PTX 135, at 1252 (Zakelj)).

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[19] It is irrelevant that the claimed amount of 100 mg EDTA was twenty times the previous commercial embodiment—in the Inactive Ingredient Guide—of 5 mg, because the literature had already indicated that up to 175 mg EDTA could be used safely. "Nothing in the statute or our case law requires [defendant] to prove obviousness by starting with a prior art commercial embodiment and then providing motivation to alter that commercial embodiment." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737 (Fed. Cir. 2013).

However, a person of ordinary skill in the art would understand that EDTA can be used in at least two ways: as a chelator of calcium and as a permeability enhancer. These publications only discussed EDTA's use in high doses as an "Absorption Enhancer" to spread the tight junctions. Van Hoogdalem tested rat tissue for intestinal separation after cleansing the tissue of calcium. (Tr. 2A.56:22-57:25). Muranishi addressed only "permeation enhancers" that "promote the intestinal absorption of impermeable drugs." (PTX 80, at 2). Zakelj sought to test methods of "increas[ing] paracellular permeability . . . [by] depletion of extracellular [calcium]." (PTX 175, at 1252). He stated that the lowest dose found to cause statistically significant separation of the tight junctions was 2 millimoles. (*Id.* at 1251). The claimed amount of 100 mg is equivalent to 0.3 millimoles. (Tr. 1B.30:14-17). In fact, Plaintiffs even cited Zakelj to FDA as evidence that its formulation containing 0.3 millimoles was safe, arguing that "EDTA is known to enhance paracellular transport at concentrations much greater than two millimolar in vitro."[20] (DTX 97, at 306, 311; Tr. 4A.129:3-10).

In sum, these references did not opine on, or even discuss, the claimed use of EDTA as a chelator of stray calcium. Rather, they came to the uncontroversial conclusion that using high doses of EDTA to spread the paracellular tight junctions is undesirable. Reading these references so broadly as to suggest that all uses of EDTA are "damaging" or "inappropriate" is inconsistent with the weight of the literature. (*See, e.g.*, Tr. 2A.64:17-22). No expert witness adopted such a broad reading. Placed in context, these references suggest to the skilled artisan that EDTA is not

[20] In their post-trial proposed findings, Plaintiffs claim that the Zakelj reference "noted increased permeability and harm to cellular viability at low concentrations." (Pls.' Proposed Findings ¶ 44). Plaintiffs point to no expert testimony, nor any trial testimony, to support this assertion and it is unfounded. Zakelj said nothing of the kind.

suitable when used at doses so large that they spread paracellular tight junctions and enhance permeability. They do not suggest to the skilled artisan that EDTA in much lower doses used as a chelator of calcium will be unproductive.

Regarding the relevant concern for a person of ordinary skill in the art in 2005—whether 100 mg disodium EDTA delivered to the small intestine would be expected to deplete the calcium buffer in the fasted state, thus harming the small intestine—Plaintiffs' toxicologist Dr. Rodricks opined that the literature did not provide sufficient information to enable a person of ordinary skill to estimate the amount of residual calcium in any one location or loop of the intestines and ensure safety. (Tr. 2B.69:4-10; Tr. 2B.56:23-25). Consequently, he believed that "there would be a significant unknown about the effects" that would caution a person of skill against using EDTA. (*Id.*).

By contrast, Defendant's toxicologist Dr. Dillberger opined that, although the state of the art did not indicate exactly what dose of EDTA would have depleted calcium reserves, a skilled artisan would have known that it would have been at "much higher doses" than 100 mg. (Tr. 2A.16:10-17; Tr. 2B.56:17-19). He responded to Dr. Rodricks's concern—that a skilled artisan would be unable to estimate the concentration of residual calcium in any particular loop—by noting that a dose of EDTA would travel through the intestines at several inches per minute, such that no particular loop in the small intestine would be exposed to high levels of EDTA for a significant amount of time. (Tr. 2A.59:23-60:8). He also noted animal studies and human studies, like the *Poiger Reference*, which showed no harm to the intestines using doses of EDTA far higher than 100 mg. (Tr. 2A.17:17-25; Tr. 2A.51:6-15).

The prior art *Poiger Reference* documented the result of administering 250 mg of disodium EDTA[21] to human patients in the fasted state—the only state where there was a safety concern that EDTA would damage the tight junctions. In a patient who has fasted, the EDTA would have reached the intestines substantially in the unchelated state, like the claimed dose. (Tr. 2A.30:16-19 ("[M]ore than 95 percent of [disodium EDTA] swallowed gets down in the intestinal tract . . . .")). Yet when patients took 250 mg disodium EDTA in the fasted state, Poiger recorded neither intestinal harm nor a statistically significant increase in active ingredient absorption over administration without EDTA. This would suggest to a skilled artisan that 250 mg EDTA in the fasted state would not harmfully widen the tight junctions. It persuasively supports an inference to the skilled artisan that a far lower dose of disodium EDTA—such as the claimed dose—could be administered directly to the small intestine without harm. Accordingly, Dr. Dillberger aptly concluded that a person of ordinary skill in the art would have considered 100 mg disodium EDTA to be safe for human pharmaceutical use and that the literature did not discourage its use. (Tr. 2A.13:24-14:3).

This is also how Plaintiffs understood the literature in 2003 when they began giving EDTA to human subjects to support their new drug application to FDA. Before conducting any clinical safety evaluation on the EDTA-risedronate formulation in the fasted state, one of Plaintiffs' internal toxicologists told an Institutional Review Board—comprised of independent scientists and physicians charged with assessing the safety of early versions of ATELVIA®—that "the [100 mg] amount of EDTA selected . . . is designed to scavage any remaining divalent

[21] Poiger administered 500 mg EDTA samples. Although they were not pure disodium EDTA—they contained equal parts disodium EDTA and tetrasodium EDTA—each had at least 250 mg of unchelated disodium EDTA.

cations in the colon. This amount of EDTA is considered safe." (DTX 10, at Bates No. 487 (Clinical Protocol describing basis for conducting clinical trial in humans)). Based on the literature, Plaintiffs' primary nonclinical bisphosphonate toxicologist could not "recall ever believing that [100 mg EDTA] either was not safe or that we could not demonstrate that it was safe" as a chelator of calcium. (Tr. 2B.107:1-3). In 2003, before any clinical testing, the Institutional Review Board approved the safety of research with 100 mg disodium EDTA in human patients in the fasted state. (Tr. 2B.24:5-22). The informed consent notice to human participants did not identify in its section on "possible disadvantages and risks" that EDTA could cause intestinal damage in the fasted state at 100 mg. (DTX 10, at Bates No. 556). As Plaintiffs' head of regulatory affairs told FDA, the "100 milligram dose used in the risedronate DR tablet[] edetate[22] disodium is not expected to effect the permeability and absorption of risedronate and/or other drugs . . . by altering intestinal permeability." (Tr. 2B.126:14-20). In other words, none of Plaintiffs' toxicologists or regulatory personnel thought that the literature posed safety concerns that discouraged investigation in humans. Nor did the independent Institutional Review Board.[23] A person of ordinary skill in the art, reading the references in context, would have believed that a pharmaceutical composition containing 100 mg EDTA delivered to the small intestine without

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[22] Edetate is another name for EDTA. (Tr. 1B.138:3-4).

[23] Plaintiffs never mentioned to the human participants that very high doses of EDTA cause harmful spreading of the tight junctions as reported in Lin and Janner, nor did they mention the danger of using EDTA as a permeability enhancer as reported in Muranishi and Van Hoogdalem. Rightly so, because these studies were irrelevant. Plaintiffs were not testing permeability enhancement, nor any dose above 700 mg; rather, they were testing EDTA as a chelator at 100 mg.

food was likely safe for its intended use. Every scientist and toxicologist consulted in 2003 agreed.

Based on the publications available in 2005, the credible expert testimony,[24] and the relevant evidence, the literature did not discourage the use of EDTA in the claimed amount nor suggest that EDTA would be unproductive as a chelator of calcium in the small intestine. Accordingly, the literature did not teach away. *See Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1332 (Fed. Cir. 2008) (finding that reference criticizing speed above 5 m/s for one method of reading an optical disk (recrystalization) did not teach away from using speed above 5 m/s for a different, claimed method (laser pulses) of reading an optical disk); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1355 (Fed. Cir. 2012) (finding prior art that taught away from using conventional non-enteric coated oral dosage forms did not teach away from all non-enteric coated formulations, nor one particular claimed powder formulation); *In re Gartside*, 203 F.3d 1305, 1320 (Fed. Cir. 2000) (finding reference that taught low to moderate temperatures were undesirable for catalytic reactions did not teach away from use of all catalytic systems, nor the claimed system which used high temperatures).

[24] Dr. Dillberger's analysis was highly credible. Dr. Rodricks was not lacking in credibility, but his primary opinion was that there was uncertainty and "unknowns facing a POSA," (Tr. 2A.49:25-50:3), regarding the claimed dose of EDTA. Lack of certainty, without more, does not establish that prior art teaches away. *Warner Chilcott Co., LLC v. Teva Pharm. USA, Inc.*, --- F. App'x ---, No. 2014-1439, 2014 WL 6435042, at *6 (Fed. Cir. Nov. 18, 2014) ("Plaintiffs rely on the testimony of their experts and assert that there was uncertainty regarding the safety and efficacy of a once-monthly regimen, . . . [L]ack of certainty does not preclude a conclusion of obviousness.").

B. Long-felt, Unmet Need

A claimed invention's "satisfaction of a long-felt need" is evidence of nonobviousness. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) "[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem." *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). "[W]e look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need." *Procter & Gamble Co.*, 566 F.3d at 998.

There was a long-felt need for a drug that "took the compliance problem out of the equation."[25] Before ATELVIA® was released, over half the patients took their medicine incorrectly, and one-third failed to comply with the instruction to wait half an hour after administration before eating breakfast. (PTX 118, at 491, Figure 2 (1998 study of daily-administered alendronate)). The evidence at trial established that taking the predecessor drug ACTONEL® incorrectly would result in a dose that was ineffective because of the food effect. On the other hand, taking ATELVIA® in the fasted state—i.e. taking it incorrectly—nonetheless would result in a dose that is effective at treating osteoporosis, (PTX 188, at 272; Tr. 3A.20:10-12), even if there were additional side effects of upper abdominal pain, (*see* Tr. 3A.20:13-17).

Other products were released before the priority date that also made compliance easier, with fasting administration once weekly and once monthly rather than once daily. (*See* Joint Stipulation of Facts ¶¶ 48 (FOSAMAX® 2000), 55 (ACTONEL® 2002), 59 (BONIVA® 2005)). But the effectiveness of those formulations would not improve for a patient who either refused to fast

[25] Warner stipulated that they are "not arguing that Atelvia can be administered 'with or without food.'" (Final Pretrial Order 18, ¶ 102, Dkt. No. 207). Thus, they do not assert satisfaction of a long-felt need for a bisphosphonate that can be taken regardless of food intake. FDA has approved ATELVIA® to be administered with food only. (Joint Stipulation of Facts ¶ 75).

or could not understand the fasting rule, whether once monthly or once daily. Although ATELVIA® patients must still comply with administration rules regarding co-administered drugs that interfere with absorption, (PTX 409, at 9 (ATELVIA® label); Tr. 3A.61:2-6), it does satisfy a need for a drug that lessens the consequence of failure to comply with the feeding or fasting rules. This satisfaction of a need to take compliance out of the equation for treatment of osteoporosis is entitled to some weight.

C. Unexpected Results

An inference that a patent is not obvious may be supported by "a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). "[T]he applicant's showing of unexpected results must be commensurate in scope with the claimed range." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *see also In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.").

ATELVIA® researcher Dr. Michael McClung, who conducted a two-year study on the drug, testified that patients taking either ATELVIA® per label or contra label unexpectedly performed better than ACTONEL® per label in the second year of the study. (DTX 182, at 305; Tr. 3A.31:18-32:3). He relied on data from one bone location (lumbar spine) using one measure of bone density, which showed a statistically significant difference in patient bone density in the

ATELVIA® groups and the ACTONEL® group between year one and year two. (DTX 182, at 302-05). However, other locations (total hip and femoral neck) and other measures of bone density (urine and serum concentration) did not show statistically significant differences between year one and year two. (Tr. 3A.79:2-80:17). McClung opined that the reason for the difference in bone density was that the researchers saw the patients less frequently in year two, and were unable to remind patients of the dosing instructions, resulting in a drop in compliance. He concluded that ATELVIA® performed unexpectedly well compared to ACTONEL® in year two because the consequence of failing to comply with dosing rules for ATELVIA® was not as dire as with ACTONEL®. (Tr. 3A.37:8-10). However, he admitted that "there's no way to prove that. One cannot assess that component of compliance." (Tr. 3A.35:23-24).

This allegedly unexpected result is about essentially the same concept as the evidence of long-felt need to diminish the consequence of noncompliance. It is rendered less weighty because other measures of bone density and other locations of measurement did not show a statistically significant difference between year one and year two. (Tr. 3A.79:2-80:17). And the reason for the improvement in bone density in some samples for patients taking ATELVIA® in year two could also be due to the study's comparison of *daily* ACTONEL® to *weekly* ATELVIA®. No single head-to-head clinical study has been conducted which compared once-weekly ATELVIA® directly with once-weekly ACTONEL®. (Joint Stipulation of Facts ¶ 76). McClung acknowledged the possibility that long-term compliance with dosing rules may be easier if the patient only needs to comply once weekly rather than every day. (Tr. 3A.42:3-43:1; Tr. 3A.46:3-12; DTX 182, at 306). Thus, any improvement in patient bone density in year two may be due to

dosing frequency rather than the claimed invention.[26] "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Because these unrelated factors could equally be the reason for the observed result, and because other testing methods and locations diminished the value of the observed result, there is an absence of sufficient evidence of nexus to the patient compliance issue. Accordingly, the Court gives the evidence little weight.

D. Simultaneous Invention: The Takeda Invention

"Independently made, simultaneous inventions, made 'within a comparatively short space of time,' are persuasive evidence that the claimed apparatus 'was the product only of ordinary mechanical or engineering skill.'" *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (quoting *Concrete Appliances Co. v. Gomery*, 269 U.S. 177, 184 (1925)). "[T]hough not determinative of statutory obviousness, [simultaneous invention is] strong evidence of what constitutes the level of ordinary skill in the art." *Geo. M. Martin Co.*, 618 F.3d at 1305-06. (quoting *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000)). It "is directly tied to the level of knowledge attributable to one of ordinary skill in the art." *Ecolochem*, 227 F.3d at 1379.

In the instant case, there was a real battle by the parties about the invention by a Japanese company called Takeda. Takeda invented a drug with risedronate and disodium EDTA

[26] The Harris study addressed the safety and efficacy of once-daily ACTONEL® compared to once-weekly ACTONEL®. (PTX 166, at 763; Tr. 3A.27:4-9). It did not address the effect on compliance of moving from once-daily to once-weekly administration. (PTX 166, at 758 (All "subjects were instructed to take the study drug once a day."))

that exhibited "pharmaceutically effective absorption." Japanese Patent Application No. 2003-359,539 (DTX 35) was filed on October 20, 2003, several years before the challenged patents. The story of why Takeda did not get its patent is not a pretty picture: Proctor & Gamble used its commercial muscle to pressure Takeda to abandon its patent application to avoid its publication and stop it from becoming prior art to Proctor & Gamble's research into ATELVIA®. The pressure succeeded and the Takeda application never became prior art.

Teva sought to use this saga to show inequitable conduct, and thereby invalidate the patent. This Court, following the caution and law of the Federal Circuit on this issue, did not permit an amendment to the pleadings to proceed on the claim of inequitable conduct on the theory that killing a foreign patent application to prevent it from becoming prior art would have had to be disclosed to the patent examiner. However, this Court ruled that the evidence was admissible for any other proper purpose.

The Takeda invention "pertains to a pharmaceutical composition that is capable of preventing the effect of food or drug materials on absorption of physiologically active non-peptide substances." (*Id.* at 3). Dependent claim 10 covers "an enterically coated pharmaceutical composition internally containing" "physiologically active non-peptide substances [that] are bisphosphonates" and an "absorption promoter [that] is a chelating agent." (*Id.* at 2). It lists "examples of chelating agents" as "organic acids and salt thereof, EDTA and EGTA." (*Id.* at 12). The preferred bisphosphonate is "monosodium risedronate." (*Id.* at 9).

The Takeda application describes the food effect exhibited by compounds like bisphosphonates and tetracyclines, and instructs that chelating agents defeat the food effect by "minimizing absorption variation due to interaction with food." (*Id.* at 10). This invention is characterized by similar absorption of the active ingredient in the fasted and fed states:

absorption of the non-peptide active ingredient "when co-administered with food" is "most preferably, about 60 % or more" of absorption "on an empty stomach." (DTX 35, at 18). Although the actual Takeda product formulation used sodium citrate as a chelator, its patent application encompassed formulations containing EDTA combined with risedronate sodium with the preferred effect of absorption in the fed state that is 60% of absorption in the fasted state.

Both Plaintiffs' and Defendant's formulation scientists agreed that the pharmaceutical composition discussed in the Takeda application exhibited "pharmaceutically acceptable -- effective absorption." (Tr. 4B.75:12-13 (Dr. Davis); Tr. 1B.42:6-10 (Dr. Yates)). Takeda did not have access to any of Plaintiffs' nonpublic research (or that of its predecessor Proctor & Gamble). (Tr. 2B.137:13-18 (Technology Manager Michael Burns); 2B.140:11-141:5; DTX 52).

Plaintiffs knew that Takeda's 2003 patent application disclosed the same invention as that which Proctor & Gamble, and now Warner, intended to patent. When they discovered that Takeda was working on a risedronate product with "pharmaceutically effective absorption," it "threw the organization into a panic." (Tr. 2B.143:13-25 (Burns)). A business decision was made to pressure Takeda (one of Proctor & Gamble's business partners in Japan) to abandon its patent and its research in this area "to preserve Proctor and Gamble's future global interests." (Tr. 2B.141:18-22). Technology Manager Michael Burns stated the clear explanation: "Takeda was already doing work in this area and we had to squash it for patent reasons." (DTX 63).

Why was Proctor & Gamble thrown into a "panic" when they discovered the Takeda application? Why did they need to "squash" the Takeda application? And why was the Takeda patent application abandoned so as not to become prior art? The answer is clear: they knew that Takeda had created the same invention and would achieve priority. This strong evidence of simultaneous invention is "directly tied to the level of knowledge attributable to one of ordinary

skill in the art." *Ecolochem*, 227 F.3d at 1379. A skilled artisan would have known how to conquer the bisphosphonate food effect and achieve "pharmaceutically effective absorption."

E. Skepticism

When "noted experts express[] disbelief in" a claimed invention, such evidence would support an inference of nonobviousness. *United States v. Adams*, 383 U.S. 39, 52 (1966). Two employees at Teva resisted testing the claimed amount of EDTA. (PTX 262, at Bates No. 94478; PTX 260, at Bates No. 94391). However, there is no evidence in the record regarding the employees' scientific credentials, (Tr. 2B.8:7-10; Tr. 2B.14:1-8), and thus no evidence that they were persons of skill in the relevant art. Moreover, no evidence suggested a requisite nexus between employee skepticism and the effectiveness of the claimed invention, as distinguished from concerns regarding the cost of investing in additional research to support an inactive ingredient level above the Inactive Ingredient Guide, as believed necessary to receive FDA approval for its ANDA application. (PTX 260, at Bates No. 94392; Tr. 3B.13:8-19; Tr. 3B.29:13-15). *See Muniauction, Inc. v. Thomson Corp*., 532 F.3d 1318, 1327 (Fed. Cir. 2008). Consequently, there is an absence of evidence that skilled artisans, as defined above, were skeptical the invention would be successful as claimed, and the testimony is therefore accorded little weight. *See Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F .3d 1348, 1368 (Fed. Cir. 2013) (finding relevant the "skepticism of *skilled* artisans") (emphasis added).

Patentee Burgio's testimony that Plaintiffs' development partner Sanofi Aventis stopped funding ATELVIA®—without documentary evidence or witness testimony regarding the reason Sanofi cut funding—lacks sufficient basis to constitute skepticism about the merits of the claim.

The third proffered basis—that FDA required Plaintiffs to conduct additional testing on ATELVIA®—is minimally probative of skepticism regarding whether the invention would work

as claimed.[27] Safety testing is required for every new drug. (Tr. 2B.43:12-15; Tr. 2B.61:16-25). Requests for additional testing "reflect[] attention to the FDA's normal duties ensuring the safety and efficacy of new drugs by requiring actual data to corroborate statements in a new drug application." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

F. Failure of Others and Copying

"The purpose of evidence of failure of others is to show indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1081-83 (Fed. Cir. 2012) (internal quotation marks omitted).

Before ATELVIA® was approved and launched, Teva had produced a formulation containing 35 mg risedronate sodium and 100 mg disodium EDTA. (Tr. 3B.34:11-15). The Regulatory Affairs division chose not to test this formulation in humans because it believed that FDA would require additional research to include a level of EDTA above the Inactive Ingredient Guide in its ANDA formulation. (Tr. 3B.44:24-45:4). Teva then produced batches with 40 mg EDTA and 5 mg EDTA—for which safety research was already available, (PTX 253, at Bates No. 77147)—and tested each in humans, neither of which achieved "pharmaceutically effective absorption." (PTX 258). After ATELVIA® launched, Teva tested its 100 mg EDTA batch in

[27] So, too, the correspondence from after the priority date indicating that FDA was satisfied with EDTA's safety is of minimal relevance. (*See, e.g.*, PTX 347, at Bates No. 1777908).

humans. (Tr. 3B.44:12-17). These circumstances do not reflect difficulties understanding and implementing the technology. *See DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371-72 (Fed. Cir. 2006). Teva first produced a formulation with 100 mg EDTA, which it chose not to administer because of constraints in funding additional research believed necessary to get FDA approval. (*See* Tr. 3B.38:9-14). This was not confusion or "failure" in the application of the science. There is an absence of evidence of nexus to the claimed invention; accordingly, the evidence is due little weight.

4. Differences Between The Claims and the Prior Art

Although the elements are discussed individually in order to maintain an organized explanation of its reasoning, the Court considers the claims of the '459 and '460 patents and the prior art as a whole and without hindsight in reaching its conclusions. And, although discussed in separate sections, the Court considers the objective considerations of nonobviousness, the level of ordinary skill in the art, the scope of the prior art, and the differences between the claims and the prior art in a holistic manner. While the content and scope of the prior art have been noted in certain instances above in this opinion, the analysis of the prior art and the claimed subject matter is discussed in detail below. Citations to the record will not be repeated when the facts are discussed below.

A. The Selection of "35 mg risedronate sodium"

For the same reasons that the Court found above in its anticipation opinion, the *Brazilian Application* disclosed 35 mg risedronate sodium as an acceptable choice for the bisphosphonate dose. Thus, the claimed dose represents the selection of one of a limited subclass of named ingredients disclosed by the prior art as acceptable for a formulation. *See Merck & Co. v.*

Biocraft Labs., Inc., 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the [prior art] discloses a multitude of [1,200] effective combinations does not render any particular formulation less obvious."); *Purdue Pharma Products L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 982 (Fed. Cir. 2010) ("Purdue's main argument is that a person of skill in the art would not have selected tramadol out of the myriad other possible active ingredients . . . [But the prior art] lists tramadol as one of fourteen different opioid analgesics to use in a controlled-release formulation that provide effective blood levels for twenty-four hours. As such, [the prior art] itself renders the selection of tramadol obvious regardless whether or not the patent lists tramadol as a preferred embodiment."). There was no evidence adduced that choosing risedronate, as opposed to another bisphosphonate disclosed by the *Brazilian Application*, was necessary for the invention to work effectively. The challenged patents describe other effective formulations containing ibandronate (DTX 2, '459 patent, col. 30 (Example XI describing an embodiment of the invention containing 100 mg ibandronate)) and alendronate (DTX 2, '459 patent, col. 29 (Example X describing an embodiment of the invention containing 70 mg alendronate sodium and 100 mg disodium EDTA). In claiming 35 mg risedronate, Plaintiffs chose the most common and convenient version of one of fourteen disclosed acceptable bisphosphonates.

B. <u>The Selection of "100 mg disodium EDTA"</u>

The *Brazilian Application* did not disclose a formulation with precisely 100 mg disodium EDTA. Rather, as the Court found above, it disclosed a range between 20 and 175 mg EDTA when EDTA is paired with risedronate based on relative molar weights. The claimed amount of 100 mg EDTA is within the prior art disclosed range.

It is evidence of obviousness where "a range [is] disclosed in the prior art, and the claimed invention falls within that range."[28] *Tyco Healthcare Grp. LP v. Mut. Pharm. Co., Inc.*, 642 F.3d 1370, 1372-73 (Fed. Cir. 2011) (internal citations omitted). "Where the difference between the claimed invention and the prior art is some range or other variable within the claims, the patentee must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (internal alterations omitted). Merely "optimizing" a variable is obvious unless the result is "unexpectedly good." *Peterson*, 315 F.3d at 1330; *see also* MPEP § 2144.05 ("Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical."). The inference that a prior art range for a particular variable disclosed the claimed value to a skilled artisan, "can be rebutted if it can be shown that the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results." *Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1331 (Fed. Cir. 2008) (quoting *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006)); *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 762 F.3d 1338, 1346 (Fed. Cir. 2014). But where selection of the claimed amount within the prior art range results in "only a difference in degree from the prior art results," the claimed amount is not critical. *Galderma Labs. v. Tolmar*, 737 F.3d 737-39 (Fed. Cir. 2013).

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[28] Of course, the Court considers all evidence relevant to obviousness or nonobviousness collectively before making any determination. The burden of proof never leaves the party challenging the validity of the patent and that "burden is always the same, clear and convincing evidence." *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1076-77 (Fed. Cir. 2012) (finding no "formal burden-shifting framework").

As the Court found above in its anticipation opinion, there is clear and convincing evidence that the selection of the claimed amount of 100 mg EDTA from the prior art range of 20 to 175 mg EDTA is not critical. The expert testimony demonstrated that, due to the cellular calcium buffer, no precise ratio of EDTA to other ingredients is required to achieve its purpose of blocking calcium after a meal without harming the intestinal tight junctions. The challenged patents confirm that a range of EDTA is effective regardless of the dose of risedronate it is paired with, the type of bisphosphonate, or the location of release within the small intestine. Nor did the prior art teach away or suggest that EDTA was unsuitable for its claimed use. Although there were safety concerns using EDTA at far higher doses than necessary to be effective in the small intestine (and when using EDTA as a permeability enhancer) the weight of authority, such as the *Poiger Reference*, established that EDTA was not dangerous when used as a chelator at doses below 250 mg. This implicit knowledge in the art is confirmed by Takeda's simultaneous invention, which used EDTA as a suitable chelator of calcium to defeat the bisphosphonate food effect. There was an absence of evidence that the selection of 100 mg EDTA produced any unexpected result. No evidence established that the selection of 100 mg EDTA was better than the prior art range by more than a matter of degree.

The absence of food effect studies documenting the relative effectiveness of other doses of EDTA does not diminish the persuasiveness of the expert testimony. Even the inventor Burgio did not deny that a wide range of EDTA would work effectively depending on the location of release within the lower gastrointestinal tract. (Tr. 4A.114:25-115:4). Burgio himself declared under oath to the PTO that his formulation produced "pharmaceutically effective absorption," even though he lacked a food effect study directly comparing absorption between the fed and

fasted states. (Tr. 4B.36:5-39:4). He relied, as the Court does, on persuasive inferences derived from established scientific theory.

C. "pharmaceutically effective absorption"

The limitation is defined as: "an amount of a chelating compound high enough to significantly bind the metal ions and minerals in food but low enough not to significantly alter absorption of the bisphosphonate as compared to absorption in the fasted state. That is, absorption is similar with or without food. Given the high variability of bisphosphonate absorption, fed exposure within about 50% of fasting exposure is expected to be 'pharmaceutically effective absorption.'" As the Court found in its anticipation opinion, the *Brazilian Application* did not clearly and convincingly use this term or contain all elements within its definition.

When the prior art must be modified to reach the claimed result "a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006). "Such a suggestion may come expressly from the references themselves. It may come from knowledge of those skilled in the art that certain references, or disclosures in the references, are known to be of special interest or importance in the particular field. It may also come from the nature of a problem to be solved, leading inventors to look to references relating to possible solutions to that problem." *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir.

1996) (internal citations omitted); *see Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007).

To show a reasonable expectation of success, a skilled artisan must be motivated to do more than "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem*, 437 F.3d at 1165. "Similarly, prior art fails to provide the requisite 'reasonable expectation' of success where it teaches merely to pursue a general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* (internal citations and quotation marks omitted). "What does matter is whether the prior art gives direction as to what parameters are critical and which of many possible choices may be successful." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014). But "[o]bviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

i. Motivation to Modify

The *Brazilian Application* used EDTA to: "a) reduc[e] the formation/solubilization of insoluble complexes of bivalent [calcium and magnesium] ions with bisphosphonates, and b) increase [] permeability of the intestinal mucosa." It does not require the claimed element that "absorption is similar with or without food." The evidence at trial revealed reasons to modify the *Brazilian Application* to exclude enhancing intestinal permeability and to achieve "absorption [that] is similar with or without food."

By 2005, it was understood that altering the integrity of the tight junctions was undesirable because of the risk of bacterial infection of the more permeable intestinal membrane. The weight of the literature conclusively found that using EDTA at the very high doses necessary to enhance intestinal permeability in humans was disfavored. Thus, a person of ordinary skill in the art would have been motivated to avoid "significantly alter[ing] absorption of the bisphosphonate as compared to absorption in the fasted state."

Not only did the bisphosphonate literature as a whole discourage enhancing intestinal permeability, it also strongly favored eliminating the bisphosphonate food effect. All bisphosphonates, including ACTONEL®, FOSAMAX®, and BONIVA®, instructed patients to administer the dose without food because the cations found in food formed insoluble complexes with bisphosphonate. But some patients did not want to fast before taking their dose and other patients had trouble remembering the dosing instructions. This well-known and well-understood food effect problem would have motivated skilled artisans to seek a formulation wherein "absorption is similar with or without food."

This was not merely an abstract motivation to eliminate the food effect for bisphosphonates generally, but a motivation to use chelating agents in combination with bisphosphonates to achieve similar absorption in the fed and fasted states. AstraZeneca's *WO '111* patent suggested that pairing chelating agents with bisphosphonates would help achieve "less variation in absorption" of a bisphosphonate. The reference stated that formulations of a bisphosphonate combined with a chelating agent such as EDTA would allow for "oral administration [that] may be given during fasted or fed conditions" to "allow the patient to take

the medicament more conveniently, e.g. together with food intake."[29] (DTX 206, at 2). In other words, it explicitly suggested using a chelating agent to achieve similar absorption of bisphosphonates regardless of food intake.

So, too, the 1978 *Poiger Reference* would have motivated a person of skill in the art to modify the *Brazilian Application* to include "absorption [that] is similar with or without food." Poiger solved the tetracycline food effect in humans using EDTA solely to significantly chelate metal ions in food, without increasing absorption of the active ingredient. The result was similar absorption in the fed and fasted states, significantly better than the fed:fasted ratio of 50% assumed to be pharmaceutically effective. Tetracycline—like the active ingredient in ATELVIA®—is captured by calcium molecules when a patient has eaten, leading to negligible amounts of absorption. Poiger showed that tetracycline administered with the chelating agent disodium EDTA blocked the formation of tetracycline-calcium complexes, just as the *Brazilian Application*, Lin, and Janner suggested with bisphosphonate-calcium complexes.

A person of ordinary skill in the art, who would have understood the cause of the bisphosphonate food effect and the desire to solve it, would have been motivated by the *Poiger Reference's* success achieving "almost equivalent" absorption "irrespective of the diet" using EDTA as a chelator of calcium. Although Poiger was not within the bisphosphonate literature, it was squarely within the literature relied upon by the *Brazilian Application*. Both parties' experts agreed that a person of ordinary skill in the art would have understood that the first section of the *Brazilian Application* was about using EDTA to block the calcium in food from capturing the

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[29] Plaintiffs argues that *WO '111* would have led a person of ordinary skill in the art away from using EDTA because it cited another reference, which in turn discussed the dangers of EDTA as a permeability enhancer. This argument is not persuasive. *WO '111* explicitly suggests use of the calcium chelator EDTA.

bisphosphonate. (Tr. 1A.129:3-17 (Dr. Yates); Tr. 1A.133:9-11; Tr. 4B.87:22-25 (Davis)). A skilled artisan would know that the *Poiger Reference* and the *Brazilian Application* involve the same subject matter: using EDTA to reduce the interference caused by the calcium in food on active ingredient absorption. The *Poiger Reference* was directly pertinent to the problem the inventor was attempting to solve. (Tr. 2A.17:11-16; Tr. 1B.13:11-14 ("[T]he mechanism by which bisphosphonate absorption is reduced with calcium is actually the same mechanism by which tetracycline absorption is reduced, which is the formation of insoluble calcium complexes.")).

The motivation to use EDTA as a chelator of calcium to achieve "absorption [that] is similar with or without food" is confirmed by Takeda's simultaneous research on a dose of bisphosphonate and chelating agent intended to minimize variation in bisphosphonate absorption between the fed and fasted state.

All of these known factors would have motivated a person of ordinary skill in the art to (1) seek similar absorption of bisphosphonate regardless of food intake; (2) use EDTA solely as a chelator to bind calcium from food; and (3) avoid increasing permeability by excluding very high doses that would spread the tight junctions. The totality of the evidence establishes a motivation to modify the *Brazilian Application* to include the limitation "pharmaceutically effective absorption."

ii. <u>Reasonable Expectation of Success in Achieving Similar Absorption</u>

An "expectation of success need only be reasonable, not absolute[,] . . . [enough to] convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that [the modification] would work for its intended purpose." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Thus, the question is whether a person

skilled in the art would have had a reasonable expectation of achieving similar absorption of a bisphosphonate regardless of a patient's food intake by using EDTA as a chelator to block dietary calcium.

As the Court discussed above, a skilled artisan would have expected a relatively low dosage range of EDTA to block calcium after a meal without harmfully altering the tight junctions. As the totality of the literature indicated, and as Dr. Yates testified, a skilled artisan would have recognized that comparatively low doses of EDTA, like 75 mg, were sufficient to chelate calcium in the small intestine after a meal. A skilled artisan would also have expected that substantially more than 175 mg EDTA would be needed to alter the tight junctions. For example, the *Poiger Reference* disclosed a formula for calculating how much EDTA would be needed to block dietary calcium so that it would not interfere with absorption of an active ingredient: a one-to-one ratio of EDTA to expected calcium. Defendant's formulation scientist Dr. Yates testified that those of skill in the art routinely calculate the expected concentration of ingredients at different locations, a practice called stoichiometry. (Tr. 1B.30:18-25). To calculate the amount of EDTA necessary to bind to calcium on a one-to-one basis, a skilled artisan would need access to information regarding: (1) the amount of expected calcium in the small intestine; and (2) the amount of time the active ingredient was exposed to calcium before full absorption. This information was available to one of ordinary skill in the art in the *Mahé Reference* and the *Mitchell Reference*.[30] Poiger performed similar calculations to determine the amount of EDTA

[30] For example, the *Mahé Reference* taught that the amount of calcium is least variable and most predictable in the terminal ileum, where the exposure to calcium is a concentration of 0.1 millimolar every ten minutes after ingestion of a high-calcium drink. The *Mitchell Reference* taught that risedronate absorption took about 30 minutes in the lower gastrointestinal tract and that it could be effectively absorbed in the terminal ileum. Accordingly, risedronate released in

necessary to bind to the calcium in milk he released into the stomach. (DTX 162, at 130). Based on this literature, a person of ordinary skill would have expected a range of between 75 and 175 mg to chelate calcium without affecting tight-junction permeability.

Poiger's experimental design was not perfect for studying the difference between absorption in the fed and fasted states using EDTA: he compared EDTA delivered via capsule with EDTA in solution; he adjusted the pH of dissolved EDTA to avoid side effects of disodium EDTA; he compared different amounts of EDTA in the fed state and in the fasted state; he tested EDTA with milk rather than with food; and there is limited explanation of contrary studies. But Poiger showed that EDTA could competitively inhibit calcium from food via chelation, allowing an active ingredient—otherwise captured by calcium—to reach the bloodstream. Without EDTA, a patient in Poiger's study who fasted received more than four times the dose of the active ingredient compared to when the patient had eaten. But with EDTA, absorption of the dose in the

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the terminal ileum would encounter a concentration of about 0.3 millimolar of calcium. Applying Poiger's one-to-one ratio of EDTA to expected calcium indicates that 0.3 millimolar concentration of EDTA will significantly bind to calcium in the terminal ileum of the small intestine after a high-calcium meal. Dr. Yates testified that this amount of EDTA, 0.3 millimolar, equates to slightly more than 100 mg. (Tr. 1B.30:12-17). This amount is below that disclosed as harmful to the tight junctions by a factor of five or greater. (DTX 167, at 283 ("Ultrastructural alterations of intestinal epithelium are known to occur at EDTA concentrations of 25 [millimoles]."); *id.* at 281 ("EDTA was effective at doses of 10 mg/kg and higher."); PTX 175, at 1251 ("2 [millimoles] EDTA and higher concentrations were sufficient to provoke a statistically significant . . . increase of [intestinal] permeability," whereas lesser doses are insufficient)).

Plaintiffs argue that a skilled artisan would not use Mahé's calculation of the amount of calcium in the intestine. These arguments include that Mahé purportedly underestimated the amount of calcium based on earlier studies and also that Mahé overestimated the amount of calcium by using more calcium than in the typical breakfast. This effort to diminish Mahé as providing a reasonable expectation of success is not persuasive. A skilled artisan would have used Mahé and other references to estimate the amount of calcium. (*See* Tr. 3B.35:19-23).

fasted state was better than a fed:fasted ratio of 50%. And even with 250 mg disodium EDTA on a fasted stomach, there was no statistically significant increase in absorption in the fed state—i.e. no spreading of tight junctions.

This is powerful evidence for a skilled artisan, who could foresee success in using EDTA as a competitive calcium chelator to defeat the interference caused by dietary calcium and thus achieve similar absorption without causing intestinal harm. The fact that the dosage and form of EDTA changed between trials may have cautioned that success at the observed magnitude was not guaranteed. But Poiger's teaching regarding the use of EDTA to achieve "almost equivalent" absorption that was "constant irrespective of the diet" provided guidance about the critical parameters sufficient to give a skilled artisan a reasonable expectation of success of achieving absorption that is similar in the fed and fasted states. "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re Droge*, 695 F.3d 1334, 1337-38 (Fed. Cir. 2012). A person of ordinary skill in the art would have had a reasonable expectation of success that a dose of EDTA could reliably chelate the expected amount of calcium in the small intestine after a meal without separating the tight junctions and substantially increasing absorption. The expected result of such a formulation would be "absorption [that] is similar with or without food."

The expectation of success is not diminished by the patentee's purportedly lengthy and arduous road to achieving similar absorption regardless of food.[31] For many of the hurdles the

[31] Plaintiffs argued that the purportedly confounding effect of "solid calcium" would have prevented a reasonable expectation of success. (*See* Pls.' Pretrial Proposed Findings of Fact ¶¶ 94-96, 100-101, 136-138). However, they submitted no proposed findings of facts on "solid calcium" to the Court in their final proposed findings of fact and conclusions of law and have thereby abandoned this argument. *See In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1375 (Fed. Cir. 2007).

inventor described during his testimony, the prior art *Brazilian Application* had already posited a solution. For instance, Burgio described the challenge of finding doses of EDTA effective for chelating calcium that were also low enough to be safe, and their realization that the solution was to use an enteric coating to bypass the stomach. Compared to Ezra and Janner's teaching regarding the high doses of EDTA necessary for release in the stomach, Burgio "thought there was a better way to think about doing it. . . [to] go with a lower dose and push the actual delivery of both the bisphosphonate and the chelator to the lower GI tract," "where everybody had taught it couldn't be done." (Tr. 4A.80:11-14; Tr. 4A.116:24-117:2). However, the *Brazilian Application* had come to exactly the same conclusion years before: "This invention solves the problem encountered in the current state of the art[,] presenting an innovative technique in which the chelating agent becomes available only in the small intestine, which is the principal site of bisphosphonate absorption. The purpose of targeting the release of chelating agents into the small intestine is to eliminate the interaction of these agents with the contents of the stomach." (DTX 205, at 3). And Takeda came to the same conclusion nearly simultaneously, if not before. (DTX 35, at 7).

Regarding the choice to use less EDTA, Burgio testified that "based on the Janner and Ezra information, I would have expected that you needed much more EDTA as you go further up the GI tract into the stomach and jejunum and duodenum to get [] 'pharmaceutically effective absorption.'" (Tr. 4A.93:16-20). Here, too, the prior art *Brazilian Application* recommended the solution: lower the dose from the "extremely high (more than 100 mg/kg of body weight)" doses in Janner to less than 175 mg EDTA. The reason for this is that the "contents of the stomach also contain calcium and magnesium ions, the interaction of the contents with the chelating agents compromises the potentiating action of absorption, since a large part of the chelating agents is

'consumed' before they reach the small intestine. . . [R]elease of chelating agents only into the small intestine permits a reduction in the dosage administered for the desired result, which is increased absorption of the bisphosphonates." [32] (*Id.*).

Burgio also described how the inventors expected "pharmaceutically effective absorption" to occur in the ascending colon—where they expected calcium levels to be lowest—but that testing failed to achieve "pharmaceutically effective absorption" in the ascending colon. Release of the formulation in the ascending colon resulted in a ratio of fed to fasted absorption of 34%, whereas release in the small intestine produced a ratio of fed to fasted absorption of 73%. (PTX 352, at s3). Thus, absorption of risedronate when released in the ascending colon, although far from negligible, was "subpar" and was not "pharmaceutically effective absorption." (Pls.' Proposed Findings ¶ 8).

A skilled artisan would have reasonably expected success in choosing the prime location to release the risedronate. First, the *Mahé Reference* suggested that the level of calcium after a meal was most predictable and stable in the small intestine, particularly the ileum, and not the ascending colon. And the *Brazilian Application* suggested delivery of the chelating agent "only into the small intestine." (DTX 205, at 3). While the inventors chose to begin with the ascending

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[32] Plaintiffs argue that the *Brazilian Application* does not contain human testing data indicating that lower doses would be successful. But a full clinical study need not be conducted to show an expectation of success. *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."). Rather, the test is whether there is clear and convincing evidence that a person of ordinary skill in the art would have a reasonable expectation of success in using the treatment at issue. *Procter & Gamble Co.*, 566 F.3d at 994; *see also Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 F. App'x 289, 294 (Fed. Cir. 2011) ("A reference, however, is prior art for all that it discloses, and there is no requirement that a teaching in the prior art be scientifically tested, or even guarantee success, before providing a reason to combine. Rather, it is sufficient that one of ordinary skill in the art would perceive from the prior art a reasonable likelihood of success.").

colon, *Mahé* and the *Brazilian Application* provided a reasonable expectation of success by release in the small intestine. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014) ("The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected."). Based on the *Poiger Reference*, the *Mahé Reference*, and the expert testimony regarding a skilled artisan's knowledge of the mechanics of EDTA, there is clear and convincing evidence that a skilled artisan would have reasonably expected success using an amount of EDTA sufficient to bind calcium, without significantly affecting the permeability of the cellular membrane, such that absorption would be similar in the fed and fasted state.

V. CONCLUSION

The Court now considers, as a whole, the knowledge of one of ordinary skill in the art, the scope and content of the prior art compared to the claimed invention, and the objective considerations of nonobviousness. The parties agree that the *Brazilian Application* contains "all of the elements of the asserted claim[s]" except "pharmaceutically effective absorption." The *Brazilian Application* disclosed an enterically coated formulation containing a combination of a bisphosphonate and a chelating agent. It named the claimed "methacrylic acid" copolymer as an acceptable enteric coating, as one that releases immediately "only in the small intestine." It explicitly named the claimed ingredient risedronate sodium as an acceptable bisphosphonate and explicitly named the claimed ingredient disodium EDTA as an acceptable chelating agent. It disclosed use of an "effective quantity" of risedronate, which a person of ordinary skill would know included the most commonly prescribed and convenient dose: the claimed amount of 35 mg. And it disclosed a preferred range of disodium EDTA equivalent to between 20 and 175 mg,

which includes the claimed amount of 100 mg. The selection of 100 mg was not critical; there is no special benefit to choosing 100 mg rather than another amount within the prior art range. Instead, a wide range of levels of EDTA would be effective in blocking the calcium in food from capturing the active ingredient without increasing permeability. The literature did not teach away from using disodium EDTA, nor did it suggest using this amount of EDTA would be dangerous. It taught only that very high doses of EDTA were harmful and that using such very high doses of EDTA for the specific purpose of spreading the tight junctions was undesirable.

The *Brazilian Application* discussed two separate mechanisms to increase bisphosphonate absorption: (1) chelation, wherein EDTA binds to calcium molecules in food after a patient has eaten and blocks the calcium molecules from capturing the bisphosphonate; and (2) permeability enhancement, wherein large doses of EDTA spread the tight junctions, increasing overall intestinal absorption. As in the *Brazilian Application*, the challenged patents require "an amount of a chelating compound high enough to significantly bind the metal ions and minerals in food." However, the challenged patents also require "an amount of a chelating compound . . . low enough not to significantly alter absorption of the bisphosphonate as compared to absorption in the fasted state." Thus, the challenged patents chose one of the two methods set forth in the *Brazilian Application*.

Considering the level of skill in the art and the scope and content of the prior art, there is clear and convincing evidence that a person of ordinary skill in 2005 would have been motivated to avoid the high levels of EDTA necessary to enhance permeability because the literature taught that such "extremely high" doses were undesirable. At the same time, a skilled artisan would have known that EDTA's chelation mechanism would eliminate the bisphosphonate food effect. *WO '111* explicitly suggested that chelating agents produced less variable bisphosphonate

absorption after a meal. Lin and Janner discussed how EDTA would prevent bisphosphonate-calcium complexes—long known as the cause of the food effect—from forming. The *Brazilian Application*, too, instructed delivery "only into the small intestine" to "eliminate[] the interaction of [bisphosphonate] with the contents of the stomach," wherein the chelating agent "capture[s] the bivalent ions in preference to the bisphosphonate, permitting the bisphosphonate to remain free for absorption by the body." The experts on both sides agreed this disclosure informed a person of skill in the art that EDTA would block calcium after a meal, thus overcoming the food effect. And Takeda's simultaneous invention confirms the knowledge in the art that chelating agents like EDTA are effective at chelating calcium after a meal and achieving a similar ratio of fed:fasted bisphosphonate absorption.

The *Poiger Reference*, among others, was a strong predictor of success that EDTA could capture dietary calcium after a meal and allow an active ingredient to be absorbed without enhancing intestinal permeability. Based on Poiger's formula and the other prior art references, a skilled artisan could have predicted success using the same dosing range as claimed. And the *Mahé Reference* and the *Brazilian Application* suggested the small intestine as the likely successful delivery location. Based on these and the other references detailed above, there is clear and convincing evidence that a skilled artisan would have been motivated to modify the prior art to contain the claimed limitations and would have reasonably expected success in so doing.

The Court balances this evidence of a known, desirable use for EDTA against the evidence that ATELVIA® met a need for an osteoporosis drug that lessened the consequence of failure to fast before administration. In light of all the circumstances, some satisfaction of a need is not sufficient to outweigh the extensive evidence in the prior art showing that coadministration

of EDTA and a bisphosphonate would have the benefit of reducing the food effect and the evidence of Takeda's simultaneous invention of a formulation that would meet the need to a similar extent. *See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 883 (Fed. Cir. 1998). Weighing all relevant objective considerations, Plaintiffs' asserted objective considerations "do not, in the circumstances of this case, tip the scales of patentability." *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 36 (1966).

The asserted claims of the '459 and '460 represent the most common version of a bisphosphonate the prior art disclosed as acceptable combined with the most well-known and widely used chelating agent, as recommended by the prior art. That combination was used for a purpose that skilled artisans understood EDTA addressed: chelating calcium after a meal. "When there is . . . market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). The expected result of this identified solution was similar absorption in the fed and fasted states. That Takeda did just that—pursuing known options with identified ingredients—is why Proctor & Gamble was thrown "into a panic" and "squash[ed] [the application] for patent reasons."

The claims are thus a combination of known elements, arranged in a known way, to produce expected results. The patentee selected this combination of known ingredients, within the ranges disclosed as acceptable in the prior art, and patented the resulting blood concentration. And the specific doses of ingredients chosen from the prior art range was similarly unremarkable. Such a combination "is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 550 U.S. at 420; *see Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (finding obvious the patentee's selection of amount of omeprazole

from a range and class of active ingredients in the prior art combined with a particular amount of sodium bicarbonate from a range and class of buffering agents disclosed in same prior art, and claiming the resulting expected serum concentration of omeprazole). Applying the clear and convincing standard of proof, claim 16 of the '459 patent and claim 20 of the '460 patent, considered as a whole, are obvious.

An appropriate Order will issue.

/s/ Faith S. Hochberg
Hon. Faith S. Hochberg, U.S.D.J.

CLOSED

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

WARNER CHILCOTT COMPANY, LLC, et al., Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Case No. 11-6936 (FSH) **JUDGMENT ORDER** Date: March 4, 2015

FINAL JUDGMENT ORDER

This matter having come before the Court upon the Amended Complaint (Case No. 11-6936, ECF No. 76) of Warner Chilcott Co., LLC, and Warner Chilcott (US), LLC, (collectively "Plaintiffs");

it appearing that Plaintiffs allege in Count I of the Amended Complaint that Defendant Teva Pharmaceuticals USA, Inc.'s filing of Abbreviated New Drug Application No. 20-3217 constituted an act of statutory infringement of U.S. Patent No. 7,645,459 (the "'459 patent") pursuant to 35 U.S.C. § 271(e)(2)(A); and that Plaintiffs allege in Count II of the Amended Complaint that Defendant Teva Pharmaceuticals USA, Inc.'s filing of Abbreviated New Drug Application No. 20-3217 constituted an act of statutory infringement of U.S. Patent No. U.S. Patent No. 7,645,460 (the "'460 patent") pursuant to 35 U.S.C. § 271(e)(2)(A);

it appearing Defendant Teva filed an Answer and Counterclaims to the Amended Complaint, asserting counterclaims for a declaratory judgment of invalidity and non-infringement of the '456 and '460 patents (ECF No. 82);

it appearing the Court conducted a non-jury trial on July 14, 15, 16, 17, and 18, 2014, regarding the validity of claim 16 of the '459 patent and claim 20 of the '460 patent (the "asserted claims");

it appearing the parties have dismissed without prejudice their respective claims and counterclaims pertaining to U.S. Patent No. 8,246,989 and all claims of the '459 and '460 patents except the asserted claims;

the Court having had the opportunity to consider the trial evidence; for the reasons set forth in the Findings of Fact and Conclusions of Law dated March 4, 2015, the Court having found that Defendant has not proven its invalidity defense of anticipation by clear and convincing evidence with respect to claim 16 of the '459 patent and claim 20 of the '460 patent; and the Court having found that Defendant has proven its invalidity defense of obviousness by clear and convincing evidence with respect to claim 16 of the '459 patent and claim 20 of the '460 patent; therefore, the Court having ruled in favor of Defendant;

IT IS this 4th day of March, 2015, hereby

ORDERED AND ADJUDGED:

For the reasons set forth in the Court's Findings of Fact and Conclusions of Law dated March 4, 2015,

1. Claim 16 of the '459 patent and claim 20 of the '460 patent are not invalid as anticipated under 35 U.S.C. § 102;

2. Claim 16 of the '459 patent and claim 20 of the '460 patent are invalid for obviousness under 35 U.S.C. § 103;

3. All requests for relief in Plaintiff's Amended Complaint are denied;

4. Defendant Teva's First and Third Counterclaims, for declaratory judgment of

invalidity of the '459 patent and '460 patent, are granted with respect to claim 16 of the '459 patent and claim 20 of the '460 patent;

5. Pursuant to Fed. R. Civ. P. 58, Final Judgment is entered in favor of Defendant and against Plaintiffs;

6. In the event Plaintiffs file an appeal from this Final Judgment, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d), relating to claims that this case is exceptional under 35 U.S.C. § 285, shall be considered timely filed if filed and served within thirty (30) days after final disposition of any such appeal; and

7. In the event Plaintiffs do not file an appeal from this Final Judgment, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d), relating to claims that this case is exceptional under 35 U.S.C. § 285, shall be considered timely filed if filed and served within 30 days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4.

Dated: March 4, 2015

IT IS SO ORDERED

/s/ Faith S. Hochberg
Hon. Faith S. Hochberg, U.S.D.J.

U 7346838

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 19, 2012

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *7,645,459*
ISSUE DATE: *January 12, 2010*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

T. WALLACE
Certifying Officer

WC v. Amneal, Teva, Ranbaxy (DNJ 11-5989, 11-6936, 12-2474)
DTX-0002

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(12) **United States Patent**
Dansereau et al.

(10) **Patent No.: US 7,645,459 B2**
(45) **Date of Patent: *Jan. 12, 2010**

(54) **DOSAGE FORMS OF BISPHOSPHONATES**

(75) Inventors: **Richard John Dansereau**, Cincinnati, OH (US); **David Ernest Burgio, Jr.**, Liberty Township, OH (US)

(73) Assignee: **The Procter & Gamble Company**, Cincinnati, OH (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 726 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/106,816**

(22) Filed: **Apr. 15, 2005**

(65) **Prior Publication Data**

US 2005/0260262 A1 Nov. 24, 2005

Related U.S. Application Data

(60) Provisional application No. 60/573,881, filed on May 24, 2004.

(51) **Int. Cl.**
A61K 9/28 (2006.01)
A61K 9/20 (2006.01)
A61K 31/675 (2006.01)

(52) **U.S. Cl.** **424/474**; 424/465; 424/468; 514/89

(58) **Field of Classification Search** 424/474
See application file for complete search history.

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(57) **ABSTRACT**

Oral dosage forms of a bisphosphonate comprised of a safe and effective amount of a pharmaceutical composition comprising a bisphosphonate, a chelating agent, and, means for effecting delayed release of the bisphosphonate and the chelating agent in the lower gastrointestinal tract provide delivery of the pharmaceutical composition to the lower gastrointestinal tract of the mammal subject and pharmaceutically effective absorption of the bisphosphonate with or without food or beverages. The present invention substantially alleviates the interaction between bisphosphonates and food or beverages, which interaction results in the bisphosphonate active ingredient not being available for absorption. The resulting oral dosage form may thus be taken with or without food. Further, the present invention effects delivery of the bisphosphonate and the chelating agent to the lower GI tract, substantially alleviating the upper GI irritation associated with bisphosphonate therapies. These benefits simplify previously complex treatment regimens and can lead to increased patient compliance with bisphosphonate therapies.

24 Claims, No Drawings

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DOSAGE FORMS OF BISPHOSPHONATES

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority under Title 35, United States Code 119(e) from Provisional Application Ser. No. 60/573,881, May 24, 2004

FIELD OF THE INVENTION

The present invention relates to oral dosage forms of a bisphosphonate comprised of a safe and effective amount of a pharmaceutical composition comprising a bisphosphonate, a chelating agent for enabling administration of the bisphosphonate active ingredient with food or beverages, means for effecting delayed release of the bisphosphonate and the chelating agent in the lower gastrointestinal tract, and one or more pharmaceutically-acceptable excipients. The oral dosage forms of the invention provide delivery of the pharmaceutical composition to the lower gastrointestinal tract of the mammal subject and provide pharmaceutically effective absorption of the bisphosphonate when administered with or without food or beverages. The present invention further relates to a method of treating or preventing diseases characterized by abnormal calcium and phosphate metabolism comprising administering to a human or other mammal in need thereof the oral dosage form described herein.

BACKGROUND OF THE INVENTION

Bisphosphonates were first developed to complex calcium in hard water to improve detergent performance. Bisphosphonates have since been found to be useful in the treatment and prevention of diseases or conditions characterized by abnormal calcium and phosphate metabolism. Such conditions may be divided into two broad categories:

1. Conditions which are characterized by anomalous mobilization of calcium and phosphate leading to general or specific bone loss or excessively high calcium and phosphate levels in the fluids of the body. Such conditions are sometimes referred to herein as pathological hard tissue demineralization.
2. Conditions which cause or result from deposition of calcium and phosphate anomalously in the body. These conditions are sometimes referred to herein as pathological calcifications.

The first category includes osteoporosis, a condition in which bone hard tissue is lost disproportionately to the development of new hard tissue. Essential quantities of cancellous bone are lost, and marrow and bone spaces become larger, resulting in reduced cancellous bone strength. Bone also becomes less dense and fragile. Osteoporosis can be subclassified as senile, drug induced (e.g., adrenocorticoid, as can occur in steroid therapy), disease induced (e.g., arthritic and tumor), etc., however the manifestations are similar. Another condition in the first category is Paget's disease (osteitis deformans). In this disease, dissolution of normal bone occurs, which is then haphazardly replaced by soft, poorly mineralized tissue such that the bone becomes deformed from pressures of weight bearing, particularly in the tibia and femur. Hyperparathyroidism, hypercalcemia of malignancy, and osteolytic bone metastasis are conditions also included in the first category.

The second category, involving conditions manifested by anomalous calcium and phosphate deposition, includes myositis ossificans progressiva, calcinosis universalis, and such

afflictions as arthritis, neuritis, bursitis, tendonitis, and other inflammatory conditions which predispose involved tissue to deposition of calcium phosphates.

Bisphosphonates tend to inhibit the resorption of bone tissue, which is beneficial to patients suffering from excessive bone loss. However, many of the early bisphosphonates, such as ethane-1,1-diphosphonic acid (EHDP), propane-3-amino-1-hydroxy-1,1-diphosphonic acid (APD), and dichloromethane diphosphonic acid (Cl_2MDP), have the propensity of inhibiting bone mineralization when administered at high dosage levels. Although more biologically potent bisphosphonates exist, which can be administered at lower dosage levels (such as 1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate), alendronate, ibandronate, and zoledronate), oral administration of bisphosphonates sometimes results in patient complaints shortly after dosing. These complaints are usually characterized by the patients as heartburn, esophageal burning, pain and/or difficulty upon swallowing, and/or pain existing behind and/or mid-sternum. It is hypothesized that this irritation results from the bisphosphonate tablet adhering to epithelial and mucosal tissues, resulting in the topical irritation thereof. In order to avoid potential upper gastrointestinal irritation, patients taking bisphosphonates are instructed to take their medication with a full glass of water, and to remain upright for at least thirty minutes after taking an oral dose of a bisphosphonate.

It is known that oral doses of bisphosphonates are poorly absorbed (less than 1% of the oral dose) in the gastrointestinal (GI) tract. See Ezra et al., Adv. Drug Del. Rev. 42: 175-95 (2000). Several approaches have been suggested for increasing absorption of oral bisphosphonates throughout the GI tract. These approaches include modifying the permeability properties of the intestinal mucosa (e.g., through the use of absorption enhancers), or altering the physical or chemical properties of the bisphosphonate compounds themselves (e.g., through prodrugs).

While the use of absorption enhancers, such as ethylenediaminetetraacetic acid (EDTA), that increase intestinal permeability at high doses, has been proposed as a means of increasing absorption of oral bisphosphonates, the applicability of EDTA as an agent in human pharmacotherapy has been thought to be "impossible" in light of the effects of EDTA on mucosal integrity. Ezra et al., Adv. Drug Del. Rev. 42: 185 (2000). Still others have concluded that the high amount of EDTA required to effect an increase in GI absorption would exclude the agent as a candidate for use in oral bisphosphonate therapies. See Janner et al., Calcif. Tissue Int. 49: 280-83 (1991).

While the primary site of bisphosphonate absorption is the small intestine, bisphosphonates such as risedronate have similar absorption throughout the small intestine independent of where it was delivered. See Mitchell et al., Pharm Res., Vol. 15, No. 2: 228-232 (1998). Thus targeted delivery of the bisphosphonate alone to the small intestine would not increase absorption or efficacy of the bisphosphonate. However, others have attempted to increase the absorption of bisphosphonates by increasing the permeability of the intestinal mucosa through delivery of microparticles of chelating agents and bisphosphonate to the reported site of absorption (BR2001-006601).

Bisphosphonates such as risedronate and alendronate have been approved by a number of regulatory agencies as being effective in the treatment of various bone pathologies. However, interactions between bisphosphonates and foods and minerals (especially cations like calcium, magnesium, aluminum, and iron-containing foods or supplements) cause less of the bisphosphonate to be available for absorption. For

example, in Mitchell et. al., Br. J. Clin. Pharmacol. 48: 536-542 (1999), it was demonstrated that administration of risedronate within 30 minutes of a meal reduced the amount absorbed by 50% compared to administration in the fasting state. In order to reduce this food effect, the labeling of oral bisphosphonate products instruct patients to take their medication at least thirty minutes or in the case of Ibandonate sixty minutes, before the first food of the day, and are instructed to take their calcium supplements at another time of the day, or on a day when they are not taking an oral dose of a bisphosphonate. These dosing instructions can seem complex and inconvenient to the patient, which can lead to poor patient compliance.

There is an ongoing need to develop an oral dosage form of a bisphosphonate which can be taken with or without food or beverages (i.e. has pharmaceutically effective absorption regardless of food or beverage intake), at the preference of the patient, and which does not produce upper gastrointestinal irritation.

It has been found that a pharmaceutical composition comprising a bisphosphonate, a sufficient amount of chelating agent to bind the ions and minerals in food, and a means for effecting delayed release of the bisphosphonate and the chelating agent in the lower gastrointestinal tract is useful in providing an oral dosage form which provides delivery of the bisphosphonate to the lower gastrointestinal tract, as well as pharmaceutically effective absorption of the bisphosphonate when administered with or without food or beverages. The oral dosage forms of the present invention may be taken with or without food or beverages, thus simplifying the bisphosphonate treatment therapy and leading to increased patient compliance and convenience. Further, the oral dosage forms of the invention provide for delayed release of the bisphosphonate and the chelating agent in the lower gastrointestinal tract, which may alleviate the upper gastrointestinal irritation experienced with other oral bisphosphonate dosage forms and the need to remain upright for thirty minutes post-dose administration.

SUMMARY OF THE INVENTION

The present invention relates to an oral dosage form of a bisphosphonate active ingredient comprising a safe and effective amount of a pharmaceutical composition comprising:

(a) a bisphosphonate;

(b) from about 10 mg to about 1000 mg of a chelating agent; and

(c) a delayed release mechanism to deliver the bisphosphonate and the chelating agent in the lower gastrointestinal tract.

The dosage forms of the present invention provide delivery of the bisphosphonate and the chelating agent to the lower gastrointestinal tract of the mammal subject and pharmaceutically effective absorption of the bisphosphonate active ingredient when administered with or without food or beverages.

The present invention substantially alleviates the interaction between bisphosphonates and food, which interaction results in decreased absorption of the bisphosphonate active ingredient. The resulting novel oral dosage form may thus be taken with or without food or beverages, which simplifies previously complex treatment regimens and can lead to increased patient compliance with bisphosphonate therapies and if the patients are compliant their disease can be better treated. The invention further alleviates the potential for upper gastrointestinal irritation associated with immediate release oral dosage forms of bisphosphonates, by delaying release of the bisphosphonate active ingredient until the bisphosphonate and the chelating agent reach the lower gastrointestinal tract.

The present invention further relates to a method of treating or preventing diseases characterized by abnormal calcium and phosphate metabolism comprising administering to a human or other mammal in need thereof the oral dosage form described herein.

The invention further relates to a kit comprising one or more oral dosage forms of the present invention and means for facilitating compliance with methods of this invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Usage of Terms

The term "bolus" as used herein means that release of a significant amount of the bisphosphonates and/or chelating agent is achieved at the site of initiation/release.

The terms "continuous" or "continuously," as used herein, mean at regular specified intervals. For example, a continuous schedule according to a dosing regimen of once weekly means that the active is given one time per week for an unspecified period of time or for as long as treatment is necessary.

The term "nutrient," as used herein, means any nutritional or dietary supplement including but not limited to vitamins, minerals, amino acids, herbs or other botanicals, or concentrates, metabolites, constituents, extracts, or combinations of the same.

The term "pharmaceutical composition," as used herein, means an oral dosage form comprised of a safe and effective amount of a bisphosphonate active ingredient and one or more pharmaceutically-acceptable excipients including at least one chelating agent. The pharmaceutical compositions described herein are comprised of from 0.5% to 75%, preferably from 1% to 40% of a bisphosphonate active ingredient and from 25% to 99.5%, preferably from 60% to 99% of pharmaceutically-acceptable excipients including at least one chelating agent.

The term "safe and effective amount," as used herein, means an amount of a compound or composition high enough to significantly positively modify the symptoms and/or condition to be treated, but low enough to avoid serious side effects (at a reasonable risk/benefit ratio), within the scope of sound medical judgment. The safe and effective amount of active ingredient for use in the method of the invention herein will vary with the particular condition being treated, the age and physical condition of the patient to be treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient being employed, the particular pharmaceutically-acceptable excipients utilized, and like factors within the knowledge and expertise of the attending physician.

The term "sustained release" means that the bisphosphonate and/or chelating agent are not substantially released at the site of initiation but continues to be released from the initiation site throughout the remainder of the GI tract.

The term "pharmaceutically effective absorption" as used herein means an amount of a chelating compound high enough to significantly bind the metal ions and minerals in food but low enough not to significantly alter absorption of the bisphosphonate as compared to absorption in the fasted state. That is, absorption is similar with or without food. Given the high variability of bisphosphonate absorption, fed exposure within about 50% of fasting exposure is expected to be pharmaceutically effective absorption.

The term "oral dosage form," as used herein, means any pharmaceutical composition intended to be administered to the lower gastrointestinal tract of a human or other mammal via the mouth of said human or other mammal. For the purposes of the present invention, the delivered form can be in the form of a compressed tablet containing granules or particles of a bisphosphonate and a chelating agent, a capsule (e.g., soft gelatin or hard gelatin, consisting of starch, or hydroxypropylmethylcellulose) which contains beads, particles, or suspensions of the bisphosphonate and the chelating agent, or a dry mix containing granules or particles of bisphosphonate and chelating agent for making a reconstituted suspension in water (e.g., a sachet).

The term "unit dose" or "unit dosage" means a dosage form containing an amount of pharmaceutical active or nutrient suitable for administration in one single dose, according to sound medical practice. The present invention is particularly useful for the administration of unit doses in the form of tablets and capsules.

The term "gastrointestinal tract" or "GI tract," as used herein, relates to the alimentary canal, i.e., the musculomembranous tube about thirty feet in length, extending from the mouth to the anus. The term "upper gastrointestinal tract," as used herein, means the buccal cavity, the pharynx, the esophagus, and the stomach. The term "lower gastrointestinal tract," as used herein, means the small intestine and the large intestine.

The term "small intestine," as used herein, means the part of the lower gastrointestinal tract consisting of the duodenum, the jejunum, and the ileum, i.e., that portion of the intestinal tract just distal to the duodenal sphincter of the fundus of the stomach and proximal to the large intestine.

The term "large intestine," as used herein, means the part of the lower gastrointestinal tract just distal to the small intestine, beginning with the cecum, including the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum.

Bisphosphonate Active Ingredient

The terms "bisphosphonate" and "diphosphonate," as used herein, include acids, salts, esters, hydrates, polymorphs, hemihydrates, solvates, and derivatives thereof. The bisphosphonates of the present invention include those preferred compounds containing a nitrogen atom. Non-limiting examples of bisphosphonates useful herein include the following: 1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate) as described in U.S. Pat. No. 5,583,122, to Benedict et al., issued Dec. 10, 1996; U.S. Pat. No. 6,410,520 B2, to Cazer et al., issued Jun. 25, 2002; 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronic acid or alendronate) as described in U.S. Pat. No. 4,621,077, to Rosini et al., issued Nov. 4, 1986; U.S. Pat. No. 6,281,381 B1, to Finkelstein et al., issued Aug. 28, 2001; U.S. Pat. No. 6,008,207, to Brenner et al., issued Dec. 28, 1999; U.S. Pat. No. 5,849,726, to Brenner et al., issued Dec. 15, 1998; U.S. Pat. Pub. 2001/0021705 A1, by Brenner et al., published Sept. 13, 2001; U.S. Pat. No. 4,922,007, to Kieczykowski et al., issued May 1, 1990; U.S. Pat. No. 5,019,651, to Kieczykowski, issued May 28, 1991; 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate) as described in U.S. Pat. No. 4,639,338, to Stahl et al., issued Jan. 27, 1987; (4-chlorophenyl)thiomethane-1,1-diphosphonic acid (tiludronate) as described in U.S. Pat. No. 4,876,248 to Breliere et al., issued Oct. 24, 1989; 1,1-dichloromethylene-1,1-diphosphonic acid (clodronate) as described in U.S. Pat. No. 3,422,021; cycloheptylaminomethylene-1,1-bisphosphonic acid (cimadronate), as described in U.S. Pat. No. 4,970,335, to

Isomura et al., issued Nov. 13, 1990; 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid (ibandronate), which is described in U.S. Pat. No. 4,927,814, issued May 22, 1990; 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-bisphosphonic acid (zoledronate); and 1-(N-phenylaminothiocarbonyl)methane-1,1-bisphosphonic acid.

In one embodiment of the invention, the bisphosphonate is selected from the group consisting of risedronate, alendronate, pamidronate, tiludronate, cimadronate, ibandronate, clodronate, zoledronate, and salts, esters, hydrates, hemihydrates, polymorphs, and solvates thereof, and combinations thereof.

It should be noted that the terms "bisphosphonate" and "bisphosphonates," as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts, esters, hydrates, polymorphs, hemihydrates, solvates, and derivatives of these materials.

Non-limiting examples of bisphosphonate salts useful herein include those selected from the group consisting of alkali metal, alkaline metal, ammonium, and mono-, di-, tri-, or tetra-C_1-C_{30}-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, and ammonium salts.

The amount of bisphosphonate active ingredient contained in the oral dosage forms of the present invention will depend on the particular bisphosphonate selected and the continuous dosing schedule upon which the bisphosphonate is dosed to the patient. Continuous dosing schedules of daily, weekly, twice monthly, three times per month, and once monthly are non-limiting examples of dosing regimens suitable for use with the oral dosage forms of the present invention. The terms "three times per month" or "thrice monthly" mean that an oral dosage form is administered thrice, i.e., three times, during a monthly calendar period. In a thrice monthly schedule, the oral dosage forms may be administered on three consecutive days, or once about every nine to eleven days. The terms "twice per month" or "twice monthly" mean that an oral dosage form is administered twice, i.e., two times, during a monthly calendar period. In a twice monthly regimen, the oral dosage forms may be administered on consecutive days or once about every fourteen to sixteen days. The terms "monthly" or "once monthly" mean that an oral dosage form is administered once, i.e., one time during a monthly calendar period, that is, about every 28 to 31 days.

The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Mixed nomenclature is currently in use by those of ordinary skill in the art, for example reference to a specific weight or percentage of a bisphosphonate active ingredient is on an anhydrous monosodium salt basis for risedronate and on an anhydrous free acid basis for Alendronate. For the present invention, the phrase "about 35 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an anhydrous monosodium salt basis" means that the amount of the bisphosphonate compound selected is calculated based on about 35 mg of anhydrous risedronate monosodium salt. The phrase "about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an anhydrous acid basis" means that the amount of the bisphosphonate compound selected is calculated based on about 70 mg of anhydrous alendronic acid.

Generally, the oral dosage forms of the present invention will contain from about 1 mg to about 500 mg of a bisphosphonate on an anhydrous weight basis. When the bisphosphonate is dosed on a daily basis, the oral dosage form contains from about 1 mg to about 100 mg bisphosphonate on an anhydrous weight basis. When the bisphosphonate is dosed on a weekly basis, the oral dosage form contains from about 10 mg to about 200 mg bisphosphonate on an anhydrous weight basis. When the bisphosphonate is dosed on a twice monthly basis, the oral dosage form contains from about 20 mg to about 300 mg bisphosphonate on an anhydrous weight basis. When the bisphosphonate is dosed three times per month, the oral dosage form contains from about 15 mg to about 250 mg bisphosphonate on an anhydrous weight basis. When the bisphosphonate is dosed on a monthly basis, the oral dosage form contains from about 50 mg to about 500 mg on an anhydrous weight basis.

When the bisphosphonate active ingredient is risedronate, a daily oral dosage form of the present invention contains from about 1 mg to about 10 mg risedronate on a risedronate anhydrous monosodium salt basis. A weekly oral dosage form contains from about 10 to about 50 mg risedronate on a risedronate anhydrous monosodium salt basis. A twice monthly oral dosage form contains from about 20 to about 100 mg risedronate, preferably about 75 mg on a risedronate anhydrous monosodium salt basis. An oral dosage form that is administered three times per month contains from about 15 to about 75 mg risedronate, preferably about 50 mg risedronate on a risedronate anhydrous monosodium salt basis. A monthly oral dosage form contains from about 50 to about 200 mg risedronate, preferably from about 100 to about 175 mg risedronate, and more preferably about 150 mg risedronate on a risedronate anhydrous monosodium salt basis.

Chelating Agent

The term "chelating agent," as used herein, means a molecule containing two or more electron donor atoms that can form coordinate bonds to a single metal ion. The term "chelating agent" is understood to include the chelating agent as well as salts thereof. For example, the term "chelating agent" includes citric acid as well as its salt forms.

The most common and widely used chelating agents coordinate to metal atoms through oxygen or nitrogen donor atoms, or both. Other less common chelating agents coordinate through sulfur in the form of —SH (thiol or mercapto) groups. After the first coordinate bond is formed, each successive donor atom that binds creates a ring containing the metal atom. A chelating agent may be bidentate, tridentate, tetradentate, etc., depending upon whether it contains two, three, four, or more donor atoms capable of binding to the metal atom. See Kirk-Othmer Encyclopedia of Chemical Technology (4th ed. 2001).

In homogeneous dilute solutions, the equilibrium constant for the formation of the complex from the solvated metal ion (e.g., calcium) and the chelating agent in its fully dissociated form is called the formation or stability constant, K. The practical significance of formation constants is that a high log K value means a large ratio of chelated to unchelated (or free) metal ion, when equivalent amounts of metal ion and chelating agent are present. Higher ratios (or difference if K is expressed in log units) of the chelating agent and the bisphosphonate complexation constants are preferred in order to have nearly all of the metal ion complexed to the chelating agent instead of the bisphosphonate. For example, for equal molar amounts of both bisphosphonate and the chelating agent, in order for the metal ions to be 99% complexed to the chelating agent, the chelating agent must have a log K which is at least 4 units higher than the bisphosphonate-metal ion complex. The other technique which can be used to favor the chelating agent-metal ion complex over that of the bisphosphonate-metal ion complex is to add a molar excess of the chelating agent which relies on the law of mass action to favor formation of the chelating agent-metal ion complex.

Although pH and solution concentration can affect the formation constant, in general, the log K of the chelating agent is preferably at least equal to that of the bisphosphonate. In other instances the log K of the chelating agent is 2 to 5 units higher than that of the bisphosphonate. In other instances, the chelating agent is present at a molar excess to that of the bisphosphonate. The chelating agent in such instances is present in at least a 2:1 molar ratio of the chelating agent to bisphosphonate.

The chelating agent may be soluble or insoluble in the gastrointestinal tract as long as it is readily available for complexation with metal ions in the food. In one instance a chelating agent that is soluble in the gastrointestinal tract is used because chelating agents that are poorly soluble may be too slowly available to complex a significant portion of the calcium in the coadministered food. In other instances the chelating agent should have a solubility comparable to or greater than that of the bisphosphonate so that it can be present in its complexing form at concentrations at least equal to that of the bisphosphonate,

Various classes of chelating agents are suitable for use in the present invention. Non-limiting examples of these classes include polyphosphates (e.g., sodium tripolyphosphate, hexametaphosphoric acid, sodium acid pyrophosphate, sodium pyrophosphate, tetra sodium pyrophosphate, sodium hexametaphosphate, sodium metaphosphate); aminocarboxylic acids (e.g., ethylenediaminetetraacetic acid (EDTA), 1,2-bis (2-amino-phenoxy)ethane-N,N,N'N'-tetraacetic acid (EGTA), ethylenebis(oxyethylenenitrilo)tetraacetic acid (BAPTA), N-(hydroxyethyl)-ethylenediaminetriacetic acid (HEDTA), diethylenetriaminepentaacetic acid (DTPA), N-dihydroxyethylglycine (2-HxG), ethylenebis(hydroxyphenyl-glycine) (EHPG), glutamic acid, aspartic acid, glycine, lysine); 1,3-diketones (e.g., acetylacetone, trifluoroacetylacetone, thenoyltrifluoroacetone, ascorbic acid); hydroxycarboxylic acids (e.g., tartaric acid, citric acid, malic acid, gluconic acid, ferulic acid, lactic acid, glucuronic acid); polyamines (e.g., diethylenetriamine, triethylenetriamine); aminoalcohols (e.g., triethanolamine, N-hydroxyethylethylene-diamine, aminoethylethanolamine (AEEA); phenols (e.g., disulfopyrocatechol, chromotropic acid); aminophenols (e.g., oxinesulfonic acid); Schiff bases (e.g., disalicylaldehyde 1,2-propylenediimine); tetrapyrroles (e.g., tetraphenylporphin, phthalocyanine); silicates (aluminum calcium silicate, calcium silicate, sodium aluminosilicate sodium calcium aluminosilicate (hydrates), tricalcium silicate); sulfur compounds (e.g., potassium ethyl xanate, sodium diethyldithiocarbamate, diethyl dithiophosphoric acid, thiourea, magnesium sulfate); synthetic macrocyclic compounds (e.g., hexamethyl-[14]-4,11-dieneN$_4$, 2.2.2-cryptate); polymers (e.g., polyethyleneimines, polymethacryloylacetone, poly(p-vinylbenzyliminodiacetic acid)), phosphonic acids (e.g., nitrilotrimethylenephosphonic acid, ethylenediaminetetra-(methylenephosphonic acid), hydroxyethylidenediphosphonic acid).

In one embodiment, the chelating agent is selected from the group consisting of EDTA, citric acid, malic acid, tartaric acid, lactic acid, adipic acid, succinic acid, aspartic acid, glutamic acid, lysine, sodium hexametaphosphate, and combinations thereof. In another embodiment, the chelating agent is EDTA, citric acid, or sodium hexametaphosphate.

In another embodiment of the invention, a monodentate chelating agent which often precipitate as metal ion complexes, may be used in place of a polydentate chelating agent. Suitable monodentate complexing agents include, but are not limited to, phosphates (e.g., sodium phosphate, sodium aluminum phosphate, sodium acid phosphate, dipotassium phosphate, disodium phosphate, monobasic) and carboxylic acids (e.g., acetic acid).

The amount of chelating agent present in the oral dosage form of the present invention will depend on the particular chelating agent or agents (i.e. mixtures of chelating agents) selected, the amount of bisphosphonate active ingredient present in the oral dosage form, and the specific portion of the lower GI tract where delivery of the chelating agent and/or bisphosphonate active ingredient is desired. After the ingestion of milk, it has been shown in the art that the concentration of calcium decreases over the length of the lower GI tract, beginning with the small intestine and proceeding through to the end of the large intestine. Mahe, J. et al., *Gastroileal nitrogen and electrolyte movements after bovine milk ingestion in humans*, Am. J. Clin. Nutr. 56: 410-16 (1992). Thus, for example, a lower concentration of a particular chelating agent may be required to effect delivery of the bisphosphonate to the transverse colon, as compared with the concentration of that same chelating agent required to effect delivery of the bisphosphonate to the terminal ileum, given the same dose of bisphosphonate active ingredient.

Generally, the oral dosage forms of the present invention will contain a safe and effective amount of a chelating agent suitable for achieving the desired chelating effect, that is, chelating the residual metal ions that are present in the gastrointestinal tract from food at the site of delivery without significantly affecting the absorption of the bisphosphonate had no food been present. In one embodiment, the oral dosage form contains from about 10 mg to about 1000 mg of a chelating agent per unit dose. In another embodiment, the oral dosage forms contain from about 10 mg to about 500 mg of a chelating agent per unit dose. When the chelating agent is disodium EDTA, the preferred range is from about 55 mg to about 500 mg, preferably from about 75 mg to about 250 mg per unit dose. When the chelating agent is citric acid, the preferred range is from about 100 mg to about 1000 mg, preferably from about 250 mg to about 500 mg per unit dose.

Delayed Release in the Lower Gastrointestinal Tract

A human or other mammal suffering from diseases or disorders involving calcium and phosphate metabolism can be successfully treated by the delivery of the bisphosphonate active ingredient to the lower GI tract of said human or other mammal. The novel dosage forms described herein effect delivery to the lower GI tract, and prohibit the undesired release of bisphosphonate in the mouth, pharynx, esophagus, and/or stomach, thereby prohibiting the erosion, ulceration, or other like irritation of the epithelial or mucosal layers of these tissues. In some instances, it may be desirable to effect delivery of the bisphosphonate and the chelating agent to the small intestine or a particular segment of the small intestine, (e.g., the terminal ileum). In other cases, it may be desirable to effect delivery of the bisphosphonate and the chelating agent to the entire lower GI tract or to a segment of the GI tract, beginning with delivery to the small intestine and continuing with delivery if needed to the large intestine. In yet other cases it may be desirable to effect a bolus delivery of the bisphosphonate and chelating agent to the lower GI or to specific segments of the lower GI tract. In one embodiment of the invention, delivery of the active beginning in the small intestine and continuing through to the large intestine may be accomplished through the use of sustained release formulations known to those skilled in the art. Such sustained release formulations are designed to slow the release of the bisphosphonate and the chelating agent over a specified time period, as the oral dose form progresses through the lower GI tract. In still other instances, it may be desirable to achieve delivery of the bisphosphonate and the chelating agent to the large intestine or a particular segment thereof (e.g., the ascending colon). In still other instances, it may be desirable to deliver the chelating agent and the bisphosphonate in a bolus amount to the large intestine. In still other instances, it may be desirable to deliver the chelating agent to one segment of the lower GI tract, and to deliver the bisphosphonate to a different segment of the lower GI tract. For example, it may be desirable to deliver the chelating agent to the terminal ileum and the bisphosphonate to the ascending colon.

The term "delayed release," as used herein, refers to a delivery of a bisphosphonate active ingredient and a chelating agent which is achieved by formulating the pharmaceutical composition comprising the bisphosphonate and the chelating agent so that their release will be accomplished at some generally predictable location in the lower GI tract more distal to that which would have been accomplished had there been no alteration in the delivery of the bisphosphonate and the chelating agent.

In another embodiment of the invention, the bisphosphonate and the chelating agent may be administered to a mammal subject by way of more than one oral dosage form, each of which comprises a means for delivering the contents of said oral dosage form to the lower GI tract. For example, a patient may take a unit dosage of a bisphosphonate, followed by a separate unit dose containing the chelating agent.

In yet another embodiment the chelant and bisphosphonate are released rapidly and as close to simultaneously as possible. This causes the local concentration of chelating agent to be higher in relationship to the metal ions in the food. The higher local concentration of chelating agent in the environment where the active is released may more effectively complex the metals in the food and facilitate absorption of the bisphosphonate. This can be conveniently achieved from a single tablet

Various means for targeting release of the bisphosphonate and the chelating agent in the lower GI tract are suitable for use in the present invention. Non-limiting examples of means for delivery to the lower GI tract include pH triggered delivery systems, dose forms from which the release of drug is triggered by the action of bacterial enzymes, and time dependent delivery systems.

In some cases it may be desirable to initiate release of the bisphosphonate and chelating agent primary in the duodenum and/or the jejunum. In other instances it is desirable to primarily initiate release of the bisphosphonate and chelating agent in the mid-jejunum and/or the terminal ileum. In yet other cases it may be desirable to provide a sustained release of the bisphosphonate and the chelating agent primarily in the jejunum throughout the terminal ileum. For primary colonic delivery it may be desirable to initiate release of the bisphosphonate and chelating agent in the ascending and/or transverse colon.

pH Triggered Delivery Systems

One embodiment of the present invention involves coating (or otherwise encapsulating) the bisphosphonate and the chelating agent(s) with a substance which is not broken down, by the gastrointestinal fluids to release the bisphosphonate and the chelating agent until a specific desired point in the intestinal tract is reached. In one embodiment, delayed release of the pharmaceutical composition is achieved by

coating the tablet, capsule, or particles, granules, or beads of the bisphosphonate and the chelating agent with a substance which is pH dependent, i.e., broken down or dissolves at a pH which is generally present in the lower GI tract, but not present in the upper GI tract (i.e., the mouth, buccal cavity, pharynx, esophagus, or stomach).

In some cases, it may be desirable that the bisphosphonate and the chelating agent are released at a particular location in the small or large intestine. In other cases, it may be desirable to release the bisphosphonate and the chelating agent independently at different locations within the lower GI tract. For example, it may be desirable to release the chelating agent in the ascending colon, and the bisphosphonate in the transverse colon. When targeted release of the bisphosphonate and the chelating agent together or separately in particular locations within the lower GI tract is desired, the selection of the coating material and/or the method of coating or otherwise combining the bisphosphonate and the chelating agent with the selected coating material or other pharmaceutically-acceptable excipients may be varied or altered as is described herein, or by any method known to one skilled in the art.

The ultimate site of and/or the rate of delivery in the lower GI tract can be satisfactorily controlled by one skilled in the art, by manipulating any one or more of the following:

(a) the active ingredient proper;
(b) the type and level of disintegrant;
(c) the type of coating, the type and level of excipients added to the coating and the concomitant desirable thickness and permeability (swelling properties) of the coating;
(d) the time dependent conditions of the coating itself and/or within the coated tablet, particle, bead, or granule;
(e) the particle size of the granulated active ingredient; and
(f) the pH dependent conditions of the coating itself and/or within the coated tablet, particle, bead, or granule.

In particular, solubility, acidity, and susceptibility to hydrolysis of the different bisphosphonate active ingredients, such as acid addition salts, salts formed with the phosphonic group (e.g., alkali metal salts, alkaline earth metal salts, etc.), and esters (e.g., alkyl, alkenyl, aryl, arylalkyl) may be used as guidelines for the proper choice. In addition, suitable pH conditions might be established within the coated tablets, particles, granules, or beads by adding a suitable buffer to the active ingredient in accordance with the desired release pattern.

Besides the above-mentioned variations in order to obtain the desired release pattern, the excipients may also be varied, as long as they do not affect the activity of the particular bisphosphonate selected.

One embodiment of the present invention is delivered to the lower GI tract utilizing a pH dependent enteric coating material made from a partly methyl esterified methacrylic acid polymer. The oral dosage form can be in the form of an enteric coated compressed tablet made of granules or particles of active ingredient or a gelatin capsule which contains beads or small particles of active ingredient which have themselves been enterically coated.

Any enteric coating which is insoluble at a pH below 5.5 (i.e., that generally found in the mouth, pharynx, esophagus, and stomach), but soluble at pH 5.5 or higher (i.e., that present in the small intestine and the large intestine) can be used in the practice of the present invention. Accordingly, when it is desired to effect delivery of the bisphosphonate and the chelating agent to the small intestine, any enteric coating is suitable which is wholly- or partially-insoluble at a pH below 5.5 and soluble at a pH 5.5 or above.

The enteric coating must be applied to the compressed tablet, the capsule (e.g., gelatin, starch, or hydroxypropylmethylcellulose) and/or the beads, particles or granules of active ingredient in a sufficient thickness so that the entire coating does not dissolve in gastrointestinal fluids at a pH below 5.5, but does dissolve at a pH of 5.5 or above. The dissolution or disintegration of the excipient coating generally does not occur until the entry of the coated dosage form into the small intestine.

It is expected that any anionic polymer exhibiting the requisite pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery of the bisphosphonate and chelating agent to the lower GI tract. The coating chosen must be compatible with the particular bisphosphonate active ingredient selected. The preferred polymers for use in the present invention are anionic carboxylic polymers. It is particularly preferred that the polymers are acrylic polymers, more preferably partly methyl-esterified methacrylic acid polymers, in which the ratio of free anionic carboxyl groups to ester groups is about 1:1.

A particularly suitable methacrylic acid copolymer is Eudragit L®, particularly Eudragit L 30 D-55® and Eudragit L 100-55®, manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany. In Eudragit L 30 D-55®, the ratio of free carboxyl groups to ester groups is approximately 1:1. Further, said copolymer is known to be insoluble in GI fluids having a pH below 5.5, generally 1.5-5.5, i.e., that generally present in the fluid of the upper GI tract, but readily soluble at pH above 5.5, i.e., that generally present in the fluid of the lower GI tract.

Other methacrylic acid copolymer which are suitable for use in coating the oral dosage forms and/or the granules, particles, or beads of active ingredient which can be employed in the method of treatment described herein, either alone or in combination with other coatings, is Eudragit S® and Eudragit FS30D®, manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany. Eudragit S® differs from Eudragit L 30 D-55® only insofar as the ratio of free carboxyl groups to ester groups is approximately 1:2. Eudragit S® is also, like Eudragit L 30 D-55®, substantially insoluble at pH below 5.5, but unlike Eudragit L 30 D-55®, is poorly soluble in GI fluids having a pH of 5.5-7.0, such as that present in small intestinal fluids. Eudragit S® is soluble at pH 7.0 and above, i.e., that generally present in the terminal ileum and colon.

Eudragit S® an can also be used alone as a coating which would provide delivery of the bisphosphonate active ingredient beginning primarily at the large intestine (more distal than the terminal ileum) via a delayed-release mechanism. In addition, Eudragit S®, being poorly soluble in intestinal fluids below pH 7.0, could be used in combination with Eudragit L 30 D-55®, soluble in intestinal fluids above pH 5.5, in order to effect a delayed release composition which could be formulated to deliver the active ingredient at various segments of the intestinal tract; the more Eudragit L 30 D-55® used, the more proximal release and delivery begins and the more Eudragit S® used, the more distal release and delivery begins.

The coating can, and usually will, contain a plasticizer and possibly other coating excipients such as coloring agents, surfactant, talc, and/or magnesium stearate, many of which are well known in the coating art. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially triethyl citrate, tributyl citrate, acteyltriethyl citrate, dibutyl phthalate, diethyl phthalate, polyethylene glycol, acetylated monoglycerides propylene glycol, and triacetin. Conventional coating techniques

such as fluid-bed or pan coating are employed to apply the coating. Coating thickness must be sufficient to ensure that the oral dosage form remains essentially intact until the desired site of delivery in the lower GI tract is reached.

The solid oral dosage form may be in the form of a coated compressed tablet which contains particles or granules of the bisphosphonate active ingredient and the chelating agent, or of a soft or hard capsule (e.g., gelatin, starch, or hydroxypropylmethylcellulose), coated or uncoated, which contains beads or particles of the bisphosphonate active ingredient and the chelating agent, which themselves are enterically coated.

For sustained release of the bisphosphonate and chelating agent a sustained release polymer is required to control the dissolution rate of the bisphosphonate and chelating agent from the dosage form. If the bisphosphonate and chelating agent are both soluble (defined as 33 mg/ml or greater in water) then high levels of sustained release polymers are required. Sustained release polymers include but are not limited to hydroxypropylmethycellulose, hydroxypropylcellulose and Carbomer.

A. Enteric Coated Tablets

In one embodiment of the invention, the oral dosage form includes an enteric-coated compressed tablet. Tablets are made by combining, mixing, or otherwise adding the bisphosphonate active ingredient and the chelating agent to suitable pharmaceutical excipients including, but not limited to, sucrose, maltodextrin, lactose, cellulose, microcrystalline cellulose, talc, magnesium stearate, crospovidone, starch, and sodium starch glycolate. That mixture is then compressed into a tablet utilizing various methods known to those skilled in the art. The compressed tablet is then coated with an enteric-coating material which is made with suitable pharmaceutical excipients including, but not limited to, poly(methacrylic acid, methyl methacrylate 1:1 (Eudragit L® 100), poly(methyacrylic acid, ethyl acrylate 1:1 (Eudragit L 30 D-55®, Eudragit L 100-55®), poly(methacrylic acid, methyl methacrylate 1:2 (Eudragit S®, Eudragit FS30D®), hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, shellac, cellulose acetate succinate, cellulose acetate trimellatate, polyethylene glycol 400-8000, triacetin, dibutyl phthalate, acetylated monoglycerides, triethyl citrate, talc, and iron oxide. The enteric-coating material is then applied to the compressed tablet utilizing numerous spraying techniques available to those skilled in the art.

The enteric-coating of the tablets is not soluble in the fluids of the mouth, pharynx, esophagus, or stomach, and thereby prohibits the release of the bisphosphonate and the EDTA until oral dosage form reaches the lower GI tract. For the coating method described herein using methacrylate copolymers, when the desired site of delivery is the lower GI tract, it has been found that a coating thickness of between about 10 and about 500 microns usually is required. In one embodiment of the invention, the thickness is between about 10-30 and about 50 microns. In another embodiment, the thickness is between about 200 and about 350 microns. Another way to characterize the coating is to express the amount of coating as weight gain or coating solids relative to the original tablet weight. In one embodiment of the invention the weight gain of coating solids is 5-50% of the original tablet weight, in another embodiment the coating solids weight gain is 5-15%, in yet another embodiment it is 15-30% and in another it is 30-50%

B. Enteric Coated Beads or Granules

Another oral dosage form suitable for use in the present invention consists of gelatin or starch capsules which contain enteric-coated beads or granules of the active ingredient. The gelatin or starch capsules may themselves be enteric-coated, if desired. The use of capsules which contain enteric coated beads is generally not preferred from a standpoint of manufacturing cost and difficulty. However, some active ingredients which must be given in relatively higher doses are sometimes difficult to compress into tablets. In addition, when ingested with food, tablets often sit in the stomach until the digestion of food causes the opening of the pyloric sphincter and pushes the tablet into the duodenum. When uncoated gelatin or starch capsules are used, the gelatin or starch will break down in the stomach, releasing the enteric coated beads. The beads can travel through the pylorus independently of the presence of food, and there is decreased risk of large amounts of the active ingredient sitting for any period of time in direct contact with the epithelial and mucosal tissues. As used herein, "beads" refers to particles containing the active ingredient which are prepared by applying the bisphosphonate active ingredient and the chelating agent to inert substrate spheres, or beads, preferably using a polymer film.

The substrate bead, accordingly, is used as an inert substrate to which the bisphosphonate and the chelating agent are applied. The beads may be made from one, or a mixture of, a group selected from, but not limited to, sucrose, mannitol, lactose, dextrose, sorbitol, cellulose, and starch, preferably sucrose and starch. In one embodiment of the invention, the size of the inert substrate beads is in the range of from 0.25 mm to 7.00 mm, preferably from 1.00 mm to 4.00 mm. In addition, suitable inert substrate beads may be purchased, as pre-prepared, for example, non-pareil PG beads, manufactured by Penwest, Patterson, N.Y.

The bisphosphonate active ingredient and the chelating agent must be affixed to the inert substrate beads. In one embodiment, the active ingredient and the chelating agent are affixed using a polymer film. In addition, if an active ingredient is chosen that is deliquescent, the polymer film will serve to prevent the active from picking up moisture. If the active ingredient chosen is unstable in any way, the polymer film may provide some stability. The polymer film preferably comprises a mixture of hydroxypropylmethylcellulose, ethylcellulose, polyvinylpyrrolidone, and/or hydroxypropylcellulose; and a suitable plasticizer. Plasticizers suitable for use in the film include, but are not limited to, polyethylene glycol, propylene glycol, triacetin, acetylated monoglycerides, phthalate esters, castor oil, dibutyl secabate, triethyl citrate, and selected mixtures thereof. In one embodiment, the plasticizer comprises from 5% to 40% of the polymer film, preferably from 10% to 25% of the polymer film.

The polymer film may further comprise optional fillers, pigments, and dyes as described herein above.

The polymer or polymer mix can include any combination that offers protection against moisture pickup and/or oxygen transfer, and which is designed for immediate release of the active ingredient by intestinal fluid. The amount of bisphosphonate to be applied to the inert substrate beads may vary depending on the concentration desired in the finished product. However, the weight of the applied film on the substrate bead is between about 5-50% weight gain, preferably between 5-25% weight gain. The term "weight gain," as used herein, means the weight increase as a percentage of the amount of applied solids to the substrate.

After the inert substrate beads are coated with the active ingredient and chelating agent, they must be enterically coated. The enteric coating is applied using various spray techniques known to one skilled in the art. The coating is applied to the beads of active ingredient at a thickness of about 20-350 microns, in another embodiment about 30-100 microns. The coating amount can be characterized as a weight

gain of about 10-75%, in other cases about 20-50% relative to the original weight of the beads.

It may be desired to coat the granules of the bisphosphonate active ingredient and the chelating agent instead of spraying inert substrate beads with the bisphosphonate and the chelating agent. "Granules," as used herein, means particles of active ingredient and chelating agent in combination with suitable pharmaceutically-acceptable excipients as described hereinabove. Although it is preferable to encapsulate the enteric-coated granules using starch or gelatin capsules, for administration as an oral dosage form, the granules may also be compressed into tablets.

Granules can be obtained by extrusion of a moist kneaded mass followed by spheronization and drying. Granules with a regular molding are preferred, for example, rod-shaped, cylindrical, or spherical. In one embodiment, the granules are spherical pellet-type granules, with a diameter between about 0.3 and about 1.5 mm, preferably between about 0.5 and about 1.25 mm.

Suitable pharmaceutically-acceptable excipients for making the granules to be used in the novel dosage forms described herein include, but are not limited to, lactose, mannitol, cellulose, sucrose, and starch.

The prepared granules of active ingredient and chelating agent are then coated with an enteric coating material prepared from the pharmaceutically-acceptable excipients, using various coating techniques known to those skilled in the art. The coating is applied to the granules at a thickness of about 20-350 microns, preferably about 30-100 microns. The coating amount can be characterized as a weight gain of about 10-75%, preferably about 20-50% relative to the original weight of the beads.

Bacterial Enzyme Triggered Systems

In one embodiment of the invention, delivery of the bisphosphonate and the chelating agent to the lower GI tract is achieved through the use of a bacterial enzyme triggered system. Oral dosage forms from which drug release is triggered by the action of bacterial enzymes in the colon are known in the art. Various approaches to bacterially-triggered delivery systems suitable for use in the present invention include disulfide polymers, glycosidic prodrugs, and polysaccharides as matrices/coating agents. Watts, Peter J. & Illum, Lisbeth, Drug Dev. and Indus. Pharm., 23(9): 893-917 (1997).

Further approaches to bacterially-triggered delivery systems suitable for use are disclosed in Katsuma et al., J. of Pharm. Sci. 93(5): 1287-99 (2004). In one embodiment of the invention, the colon-targeted delivery system CODES™ (Yamanouchi Pharma Technologies, Norman, Okla.) is used to deliver the bisphosphonate and the chelating agent to the colon. This system comprises a tablet core containing a bisphosphonate, a chelating agent, and a saccharide, which tablet core is coated with an acid soluble material, such as Eudragit E®, and then coated with an enteric coating, such as Eudragit L®. The enteric coating protects the dosage form from degradation in the stomach, and is subsequently dissolved in the small intestine following gastric emptying. The acid-soluble coating protects against degradation as the dosage form travels through the small intestine. When the dosage form reaches the large intestine, local microflora ferment the saccharide in the tablet core into short chain fatty acids, which then dissolve the acid-soluble coating to release the core tablet contents in the colon.

Suitable enteric coating materials include Eudragit L-100® Eudragit S®, Eudragit L 30 D-55®, Eudragit F530D® cellulose acetate phthalate, shellac, or any enteric coating material that dissolves above pH 5.5. The enteric coating is applied using various spray techniques known to one skilled in the art. The enteric coating may further comprise one or more pharmaceutically-acceptable excipients including, but not limited to, talc, triethyl citrate, polyethylene glycol, Tween 80® (polyoxyethylene sorbitan monooleate, available from Sigma Chemical CO., St. Louis, Mo.), castor oil. The enteric coating is applied to the tablet core coated in acid-soluble material to provide a weight gain of 2.5% to 40%.

Suitable acid-soluble coating materials include those materials which dissolve at a pH less than 6.0, including but not limited to Eudragit E-100®, polyvinyl acetyl diethylaminoacetate, and chitosan. The acid-soluble coating may further comprise one or more pharmaceutically-acceptable excipients. Such excipients include, but are not limited to, hydroxypropylmethylcellulose, Eudragit RS®, ethylcellulose, hydroxypropylcellulose, polyethylene oxide, polyvinylpyrrolidone, triacetin, polyethylene glycol 400, triethylcitrate, Tween 80®, and castor oil. The acid-soluble coating is applied using various spray techniques known to one skilled in the art. The coating is applied to the tablet core at a weight gain of 2.5% to 40%.

The tablet core comprises one or more saccharide in an amount of 10% to 99.9% by weight of the tablet. The action of enterobacteria in the lower GI tract causes the saccharide(s) to be degraded into shorter chain fatty acids, which then dissolve the acid-soluble coating. Suitable saccharides include, but are not limited to, lactulose, raffinose, cellobiose, stachyose, fructoligosaccharide, sucrose, glucose, xylose, fructose, maltose, galactose cellulosic, and combinations thereof.

The tablet core comprises a bisphosphonate active ingredient, a chelating agent, and may contain one or more pharmaceutically-acceptable excipients. Suitable excipients include, but are not limited to, crystalline cellulose, calcium hydrogen phosphate, polyvinylpyrrolidone, magnesium stearate, sucrose, starch, magnesium oxide, and sodium lauryl sulfate.

Time Dependent Delivery Systems

In another embodiment of the invention, delivery of the bisphosphonate and the chelating agent to the lower GI tract is achieved through the use of a time dependent delivery system. Given established transit times after gastric emptying, drug and/or chelating agent release can be targeted to the various segments of the lower GI tract. For example, in order to target release of the bisphosphonate active ingredient and the chelating agent to the colon, release should be delayed until 3-4 hours after leaving the stomach. Watts, Peter J. & Illum, Lisbeth, Drug Dev. and Indus. Pharm., 23(9): 893-917 (1997). Approaches to time dependent delivery systems suitable for use in the present invention include, but are not limited to, such devices as the Pulsincap™ (Scherer DDS, Strathclyde, U.K.), the Time Clock™ (Zambon Group, Milan, Italy), and SyncroDose™ (Penwest, Patterson, N.Y.), as well as various coatings which degrade over time to release tablet contents such as hydroxypropylmethylcellulose, hydroxypropylcellulose, or any suitable hydrogel.

In one embodiment of the invention, the time-dependent device Pulsincap™ is used to target delivery of the active ingredient and the chelating agent to the lower GI tract. The active ingredient and other excipients, including the chelating agent, are contained inside the Pulsincap™ water-insoluble capsule by means of a hydrogel plug which is covered by a water-soluble cap. The entire dose form is optionally coated in an enteric-coating material to protect the dose form from degradation while in transit through the upper GI tract. When the patient swallows the Pulsincap™ dosage form, the water-

soluble cap dissolves and exposes the hydrogel plug to gastric and/or intestinal fluids. The hydrogel cap then swells, and eventually pops out of the capsule body, thus releasing the capsule contents. Release of the capsule contents can be targeted to specific regions of the lower GI tract by modifying the hydrogel plug properties. Watts, Peter J. & Illum, Lisbeth, Drug Dev. and Indus. Pharm., 23(9): 893-917 (1997).

In one embodiment of the invention, a time dependent coating is applied over a compressed tablet and then an enteric coating is applied over the time dependent coating. This is used to target delivery of the active ingredient and the chelating agent to the lower GI tract. The active ingredient and other excipients, including the chelating agent, are contained inside the core tablet. The entire dose form is coated with a time dependent coating and then an enteric coating. The enteric-coating material is to protect the dose form from degradation while in transit through the upper GI tract. When the patient swallows the dosage form the enteric coating dissolves after the dosage form leaves the stomach and then the core tablet starts to swell. Eventually, at a predetermined time in the lower GI tract fluids, the time dependent coating will rupture and releases the contents of the core tablet in the lower GI tract. Release of the core tablet contents can be targeted to specific regions of the lower GI tract by modifying the core tablet, time dependent coating and/or the enteric coating.

Pharmaceutically-Acceptable Excipients

Pharmaceutically-acceptable excipients include, but are not limited to, polymers, resins, plasticizers, fillers, lubricants, diluents, binders, disintegrants, solvents, co-solvents, surfactants, buffer systems, preservatives, sweetener agents, flavoring agents, pharmaceutical-grade dyes or pigments, chelating agents, viscosity agents, and combinations thereof. Pharmaceutically-acceptable excipients can be used in any component in making the oral dosage form, i.e. core tablet or coating.

Flavoring agents and dyes and pigments among those useful herein include but are not limited to those described in Handbook of Pharmaceutical Excipients (4th Ed., Pharmaceutical Press 2003).

Suitable co-solvents include, but are not limited to, ethanol, isopropanol, and acetone.

Suitable surfactants include, but are not limited to, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters, simethicone emulsion, sodium lauryl sulfate, Tween 80®, and lanolin esters and ethers.

Suitable preservatives include, but are not limited to, phenol, alkyl esters of parahydroxybenzoic acid, benzoic acid and the salts thereof, boric acid and the salts thereof, sorbic acid and the salts thereof, chlorbutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben.

Suitable fillers include, but are not limited to, starch, lactose, sucrose, maltodextrin, and microcrystalline cellulose.

Suitable plasticizers include, but are not limited to, triethyl citrate, polyethylene glycol, propylene glycol, dibutyl phthalate, castor oil, acetylated monoglycerides, and triacetin.

Suitable polymers include, but are not limited to, ethylcellulose, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, and Eudragit® L 30-D, Eudragit® L 100-55, Eudragit® F530D and Eudragit® S 100 (Röhm Pharma GmbH and Co. KG, Darmstadt, Germany), and Acryl-EZE® and Sureteric® (Colorcon, Inc., West Point, Pa.).

Suitable lubricants include, but are not limited to, magnesium stearate, stearic acid, and talc.

Methods of Use

The present invention further relates to a method of treating or preventing diseases characterized by abnormal calcium and phosphate metabolism comprising administering to a human or other mammal in need thereof a safe and effective amount of a pharmaceutical composition delivered to said human or other mammal via the oral dosage forms described herein.

Diseases characterized by abnormal calcium and phosphate metabolism include, but are not limited to, osteoporosis, Paget's disease (osteitis deformans), hyperparathyroidism, hypercalcemia of malignancy, osteolytic bone metastasis, myositis ossificans progressiva, calcinosis universalis, and such afflictions as arthritis, neuritis, bursitis, tendonitis, and other inflammatory conditions which predispose involved tissue to deposition of calcium phosphates.

The oral dosage forms of the present invention are suitable for administration to a patient according to a continuous dosing interval of daily, weekly, three times per month, twice monthly, and monthly.

Kits

The present invention further comprises kits that are particularly useful for administering the oral dosage forms described herein according to a continuous dosing schedule of daily, weekly, three times per month, twice monthly, or monthly. Such kits comprise one or more oral dosage forms comprising a bisphosphonate and a chelating agent and a means for facilitating compliance with methods of this invention. Such kits provide a convenient and effective means for assuring that the subject to be treated takes the appropriate oral dosage form in the correct dosage and in the correct manner. The compliance means of such kits includes any means which facilitates administering the active according to a method of this invention. Such compliance means includes instructions, packaging, and dispensing means, and combinations thereof. The kits can also comprise a means for aiding the memory, including but not limited to a listing of the days of the week, numbering, illustrations, arrows, Braille, calendar stickers, reminder cards, or other means specifically selected by the patient. Examples of packaging and dispensing means are well known in the art, including those described in U.S. Pat. No. 4,761,406, Flora et al., issued Aug. 2, 1988; and U.S. Pat. No. 4,812,311, Uchtman, issued Mar. 14, 1989.

Optionally, the kits can comprise at least one oral dosage form comprising a bisphosphonate and a chelating agent and at least one oral dosage form of an accompanying nutrient. Preferred nutrients are calcium and/or vitamin D. Oral forms of calcium suitable for use in the present invention include capsules, compressed tablets, chewable tablets, and the like. Typical salt forms of calcium suitable for use in the present invention include but are not limited to calcium carbonate, calcium citrate, calcium malate, calcium citrate malate, calcium glubionate, calcium gluceptate, calcium gluconate, calcium lactate, dibasic calcium phosphate, and tribasic calcium phosphate. In one embodiment, kits of the present invention may include tablets comprising 400 mg to 1500 mg calcium.

The term "vitamin D," as used herein, refers to any form of vitamin D that may be administered to a mammal as a nutrient. Vitamin D is metabolized in the body to provide what is often referred to as "activated" forms of vitamin D. The term "vitamin D" can include activated and non-activated forms of vitamin D, as well as precursors and metabolites of such forms. Precursors of these activated forms include vitamin D_2 (ergocalciferol, produced in plants) and vitamin D_3 (chole-

calciferol, produced in skin and found in animal sources and used to fortify foods). Vitamins D_2 and D_3 have similar biological efficacy in humans. Non-activated metabolites of vitamins D_2 and D_3 include hydroxylated forms of vitamins D_2 and D_3. Activated vitamin D analogs cannot be administered in large doses on an intermittent schedule, due to their toxicity in mammals. However, non-activated vitamin D_2, vitamin D_3, and their metabolites may be administered in larger doses than "active" forms of vitamin D on an intermittent basis, without toxicity. In one embodiment, kits of the present invention may include tablets comprising 100 IU to 10,000 IU of vitamin D.

In another embodiment, kits of the present invention may include one or more nutrient tablets comprising both calcium and vitamin D. In a further embodiment, the unit dose of nutrient comprises about 600 mg calcium and about 400 IU vitamin D.

The following non-limiting examples illustrate the formulations, processes, and uses of the present invention.

EXAMPLES

Example I

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	143.3 mg
Triethylcitrate	6.45 mg
Talc	21.5 mg
Red Iron Oxide	0.22 mg
Simethicone emulsion (30%)	0.43 mg
Polysorbate 80	0.43 mg
Purified Water	307.7 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to the pigment suspension and mixed for at least 45 minutes. The Eudragit L 30 D-55 solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated, using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 30% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 35 mg risedronate tablets, each tablet weighing 240 mg and each containing:

Active Ingredients:	
Risedronate Sodium	35 mg*
Chelant:	
Disodium EDTA	100 mg
Excipients	
Microcrystalline cellulose	85.8 mg
Sodium starch glycolate	6 mg
Stearic acid	12 mg
Magnesium stearate	1.2 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, edetate disodium, sodium starch glycolate, and microcrystalline cellulose are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately ten minutes with the intensifier bar on. The stearic acid and magnesium stearate are screened and added to the blender. The blend is mixed for approximately 3 minutes with the intensifier bar off. The blend is compressed into tablets using a suitable tablet press.

Example II

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate sodium are prepared as described below, using a similar method set forth in Example I.

A coating composition is prepared from a lacquer containing the following excipients, per tablet:

Ingredients:	
Acryl-EZE (manufactured by Colorcon, Inc., West Point, Pa.) dry solids	200 mg
Purified Water	950 mg

A coating weight of 40% weight gain is applied by conventional pan coating to tablets containing 150 mg risedronate and 75 mg EDTA so that oval tablets, each weighing 500 mg, result. The composition of each tablet is as follows:

Active Ingredients:	
Risedronate Sodium	150 mg*
Chelant:	
Disodium EDTA	75 mg
Excipients	
Mannitol	100 mg
Starch 1500	159 mg
Silicon Dioxide	1 mg
Stearic acid	15 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Example III

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharm GmbH and Co. KG, Darmstadt, Germany)	47.8 mg
Triethylcitrate	2.15 mg
Talc	7.17 mg
Red Iron Oxide	0.07 mg
Simethicone emulsion (30%)	0.14 mg
Polysorbate 80	0.14 mg
Purified Water	102.6 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to the pigment suspension and mixed for at least 45 minutes. The Eudragit L 30 D-55 solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated, using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 10% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 35 mg risedronate tablets, each tablet weighing 230 mg and each containing:

Active Ingredients:	
Risedronate Sodium	35 mg*
Chelant:	
Disodium EDTA	100 mg
Excipients:	
Macrocrystalline cellulose	25.8 mg
Hypromellose	76.8 mg
Magnesium stearate	2.4 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, edetate disodium, hypromellose, and microcrystalline cellulose are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately twenty minutes with the intensifier bar on. Approximately 50% of the magnesium stearate is screened and added to the blender. The blend is mixed for approximately 3 minutes with the intensifier bar off and then chilsonated and milled. The remaining magnesium stearate is screened and added to the blender with the granulation. The blend is mixed for approximately 3 minutes with the intensifier bar off. The blend is compressed into tablets using a suitable tablet press.

Example IV

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	150 mg
Triethylcitrate	10 mg
Talc	30 mg
Black Iron Oxide	0.1 mg
Purified Water	250 mg

The enteric coating is prepared using the following method:

The talc and black iron oxide are added to a portion of purified water and mixed until uniform. The triethylcitrate is added with continuous mixing. The resulting pigment suspension is next passed through a screen or a suitable mill to break up agglomerates. The Eudragit L 30 D-55® is screened and then added to a suitable vessel and diluted with a portion of the purified water. The pigment suspension is then added to the diluted Eudragit suspension and mixed until uniform.

In a suitable coating pan, the compressed tablets (10 kg) containing risedronate and EDTA, described below, are warmed to about 30-35° C. The enteric coating suspension is sprayed onto the tablets at approximately 30 grams per minute. When the spray cycle is completed, the temperature is reduced and the tablets are removed and dried at 30-35° C. for approximately 1 hour.

A coating weight gain of 35% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 5 mg risedronate tablets, each tablet weighing 240 mg and each containing:

Active Ingredients:	
Risedronate sodium	5.0 mg*
Chelant:	
Disodium EDTA	75.0 mg
Excipients	
Microcrystalline cellulose	149.5 mg

-continued

Active Ingredients:	
Sodium starch glycolate	9 mg
Stearic acid	1.5 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The tablets are prepared by sieving the risedronate active ingredient and the EDTA with ½ of the microcrystalline cellulose into a twin shell blender. The blend is then mixed until uniform. Then, ½ of the stearic acid is added and the blend is mixed further. The blend is then is roller compacted and milled. The remaining microcrystalline cellulose and sodium starch glycolate are added and mixed until uniform. The remaining stearic acid is then added and mixed until adequate lubrication is achieved. Tablets are then compressed on a rotary tablet press.

Example V

Capsules Containing Enteric-Coated Particles

Capsules containing enteric-coated particles are made by preparing particles of the risedronate sodium active ingredients and EDTA, and then encapsulating them into a gelatin capsule. The particles have the following composition:

Component Active Ingredients:	mg/capsule
Risedronate Sodium	35 mg*
Chelant:	
EDTA	75 mg
Excipients	
Lactose	50 mg
Microcrystalline Cellulose	50 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

A mixture of risedronate sodium, EDTA, lactose, and microcrystalline cellulose is moistened with water and kneaded, extruded, and spheronized. The dried particles are subsequently coated with enteric coating material prepared as described in Example 13.

The enteric coating has the following composition:

Component	mg/capsule
Eudragit L 30 D-55 ®	90
Triethylcitrate	6
Antifoam AF	2
Talc	7
Water	275

The particles having the composition described above are coated in a coating column with a coating mixture having the above composition.

The enteric coating is prepared utilizing the procedure set forth in Example 13. In a suitable coating column, the particles are warmed to about 25° C. and enteric coating solution is applied to the particles by spraying a coating of 20% weight gain to the particles. When the spray cycle is completed, the air is turned off and the particles are cooled to room temperature.

The lacquered particles are powdered with talc and encapsulated using capsules (capsule size 0), with a commercial capsule filling machine.

Example VI

Bacterial Enzyme Triggered Tablets Containing Risedronate and Sodium Hexametaphosphate

Bacterial enzyme triggered tablets containing risedronate and sodium hexametaphosphate are made by preparing a two layer coating composition and compressed tablets containing risedronate and sodium hexametaphospahte and then applying said coating composition to said tablets.

The first layer (Acid Soluble Coating Layer) coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Acid Soluble Coating Layer

Ingredients:	
Eudragit E 100 ® (manufactured by Röhm Pharma GmbHand Co. KG, Darmstadt, Germany)	40.0 mg
Hydroxypropylmethylcellulose	10 mg
Talc	10 mg
Ethanol	450 mL
Purified Water	5 mL

The acid soluble coating is prepared using the following method:

A talc suspension is prepared by adding talc to approximately one-third of the purified water while mixing. The suspension is mixed for at least two hours. The Eudragit E 100 B and hydroxyproylmethylcelluse are added to the remaining water and ethanol mixture and mix until dissolved. The talc suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process.

B. Enteric Coating Suspension (second layer)

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbHand Co. KG, Darmstadt, Germany)	150 mg
Triethyl citrate	6.0 mg
Talc	15.0 mg
Red Iron Oxide	0.25 mg
Purified Water	260 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The Eudragit L 30 D-55 solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process.

The compressed tablets as described below are transferred to the coating pan and preheated with occasional jogging. The compressed tablets are coated with the Acid Soluble Coating then with the Enteric Coating Suspension using a typical pan

coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 12% for the Acid Soluble Coating and 13% for the Enteric Coating (total solids compared to that of the core tablet weight) is applied by spraying the above composition (A and B) onto compressed tablets containing risedronate and sodium hexametaphosphate prepared in Part C below.

C. Compressed Tablets Containing Risedronate and Sodium Hexametaphosphate

The Acid Soluble Coating and the Enteric Coating suspension prepared in Part A and B above is sprayed onto 35 mg risedronate tablets, each tablet weighing 500 mg and each containing:

Active Ingredients:	
Risedronate Sodium	35 mg*
Chelant:	
Sodium hexametaphosphate	150 mg
Excipients:	
Lactulose	300 mg
Stearic acid	14.5 mg
Magnesium stearate	0.5 mg
Purified Water	100.0 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, sodium hexametaphosphate, lactulose and the stearic acid are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately ten minutes with the intensifier bar on and granulated with the purifed water for 15 minutes. The mixture is dried overnight at 30° C., passed through a mill. The magnesium stearate is screened and added to the blender. The blend is mixed for approximately 3 minutes. The blend is compressed into tablets using a suitable tablet press.

Example VII

Time Dependent and Enteric Coated Tablets Containing Risedronate and Sodium Citrate

Time Dependent and Enteric Tablets containing risedronate and sodium citrate are made by preparing a two layer coating composition and compressed tablets containing risedronate and sodium citrate and then applying said coating composition to said tablets.

The first layer (Time Dependent Coating Layer) coating composition is prepared in the form of a polymer containing the following excipients, per tablet:

A. Acid Soluble Coating Layer

Ingredients:	
Ethylcellulose	40.0 mg
Dibuty Sebacate	8 mg
Toluene	250 mg
Ethyl Alcoholc	70 mg

The acid soluble coating is prepared using the following method:

A solution is prepared by adding the ethylcellulose to approximately two-thirds of the toluene:ethyl alcohol mixture while mixing. The solution is mixed for at least two hours. The dibuty sebacate is added and mixed for an additional two hours. The resulting coating solution is screened and mixed throughout the coating process.

B. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbHand Co. KG, Darmstadt, Germany)	150 mg
Triethyl citrate	6.0 mg
Talc	15.0 mg
Red Iron Oxide	0.25 mg
Purified Water	260 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The Eudragit L 30 D-55 solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process.

The compressed tablets are transferred to the coating pan and preheated with occasional jogging. The compressed tablets are coated with the Time Dependent Coating then with the Enteric Coating Suspension using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 10% for the Time Dependent Coating and 13% Enteric Coating (total solids compared to that of the core tablet weight) is applied by spraying the above composition (A and B) onto compressed tablets containing risedronate and sodium citrate prepared in Part C below.

C. Compressed Tablets Containing Risedronate and Sodium Citrate

The Acid Soluble Coating and the Enteric Coating suspension prepared in Part A and B above is sprayed onto 5 mg risedronate tablets, each tablet weighing 500 mg and each containing:

Active Ingredients:	
Risedronate Sodium	5 mg*
Chelant:	
Sodium Citrate	250 mg
Excipient	
Microcrystalline Cellulose	109.5 mg
Croscarmellose Sodium	25.0 mg
Mannitol	100 mg
Magnesium stearate	0.5 mg
Polyvinylpyrrolidone	10 mg
Purified Water	100.0 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, sodium citrate, microcrystalline cellulose, croscarmellose sodium, mannitol and polyvinylpyrrolidone are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately ten minutes with the intensifier bar on and granulated with purified water for 15 minutes. The mixture is dried overnight at 30° C., passed through a mill. The magnesium stearate is screened and added to the blender. The blend is mixed for approximately 3 minutes with the intensifier bar off. The blend is compressed into tablets using a suitable tablet press.

Example VIII

Time Dependent Delivery Tablets Containing Risedronate and EDTA

Time dependent delivery tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

A coating composition is prepared containing the following excipients, per tablet:

A. Coating Suspension

Excipients:	
Carnauba Wax	80 mg
Beeswax	35 mg
Polyoxyethylene sorbitan monooleate	11 mg
Hydroxypropylmethylcellulose	24 mg
Purified Water	500 mL

The coating is prepared using the following method:

The carnauba wax, beeswax, polyoxyethlyene sorbitan monooleate, and hydroxypropylmethylcellulose are added to the purified water at 60° C. and mixed for 3 hours. The resulting coating mixture is screened and mixed throughout the coating process. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated, using a typical pan coating process until the required quantity of coating solution (at 60° C.) has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 30% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The coating suspension prepared in Part A above is sprayed onto 35 mg risedronate tablets, each tablet weighing 500 mg and each containing:

Active Ingredients:	
Risedronate Sodium	35 mg*
Chelant:	
Disodium EDTA	150 mg
Excipients:	
Microcrystalline cellulose	50 mg
Spray Dried Lactose	245 mg
Sodium starch glycolate	15 mg
Magnesium stearate	5 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, EDTA disodium, microcrystalline cellulose, Spray dried lactose and sodium starch glycolate are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately ten minutes with the intensifier bar on. The magnesium stearate is screened and added to the blender. The blend is mixed for approximately 3 minutes with the intensifier bar off. The blend is compressed into tablets using a suitable tablet press.

Example IX

Bacterial Enzyme Triggered Tablets Containing Alendronate and Tartaric Acid

Bacterial Enzyme Triggered tablets containing alendronate and tartaric acid are made by preparing a tablet blend and compressing into tablets.

A. Compressed Tablets Containing Alendronate and Tartaric Acid

The 70 mg alendronate, each tablet weighing 680 mg and each containing:

Active Ingredients:	
Alendronate Sodium	70.0 mg*
Excipients:	
Guar Gum	300.0 mg
Hydroxypropylmethylcellulose	50.0 mg
Tartaric Acid	250.0 mg
Stearic acid	10 mg

*This amount is calculated on a alendronic acid anhydrous trihydrate basis.

Tablets having the composition set forth above are prepared as follows:

The alendronate sodium, guar gum, hydroypropylmethylcellulose and tartaric acid are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately ten minutes with the intensifier bar on. The blend is compressed into slugs on a rotary tablet press. The slugs are passed through a mill and collected. The stearic acid is added to the blender and the blend is mixed for approximately 3 minutes. The blend is compressed into tablets using a suitable tablet press.

The compressed tablets are coating with the layers described in Example VI using the same methods for coating.

Example X

Enteric-Coated Tablets Containing Alendronate and EDTA

Enteric-coated tablets containing alendronate and EDTA are made by preparing a coating composition and compressed tablets containing alendronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Excipients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	120 mg
Triethylcitrate	10 mg
Talc	10 mg
Red Iron Oxide	0.01 mg
Simethicone emulsion	0.8 mg
Purified Water	100 mg

The enteric coating is prepared using the following method:

The talc and red iron oxide are added to a portion of purified water and mixed until uniform. The triethylcitrate and the simethicone emulsion are added with continuous mixing. The resulting pigment suspension is next passed through a screen or a suitable mill to break up agglomerates. The Eudragit L 30 D-55® is screened and then added to a suitable vessel and diluted with a portion of the purified water. The pigment suspension is then added to the diluted Eudragit suspension and mixed until uniform.

In a suitable coating pan, the compressed tablets (10 kg) containing alendronate and EDTA, described below, are warmed to about 30-35° C. The enteric coating suspension is sprayed onto the tablets at approximately 30 grams per minute. When the spray cycle is completed, the temperature is reduced and the tablets are removed and dried at 30-35° C. for approximately 1 hour.

A coating weight gain of 19% (total solids) is applied by spraying the above composition onto compressed tablets containing alendronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Alendronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 70 mg alendronate tablets, each tablet weighing 300 mg and each containing:

Active Ingredients:	
Alendronate sodium	70 mg*
Chelant:	
Disodium EDTA	100 mg
Excipients:	
Microcrystalline cellulose	119.5 mg
Crospovidone	9 mg
Magnesium stearate	1.5 mg

*This amount is calculated on an alendronic acid basis.

Tablets having the composition set forth above are prepared as follows:

The tablets are prepared by sieving the alendronate active ingredient and the EDTA with ½ of the microcrystalline cellulose into a twin shell blender. The blend is then mixed until uniform. Then, ½ of the magnesium stearate is added and the blend is mixed further. The blend is then is roller compacted and milled. The remaining microcrystalline cellulose and crospovidone are added and mixed until uniform. The remaining magnesium stearate is then added and mixed until adequate lubrication is achieved. Tablets are then compressed on a rotary tablet press.

Example XI

Enteric-Coated Tablets Containing Ibandronate and Citric Acid

Enteric-coated tablets containing ibandronate and citric acid are made by preparing a coating composition and compressed tablets containing ibandronate and citric acid, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Excipients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	240 mg
Triethylcitrate	20 mg
Talc	10 mg
Titanium dioxide	1.0 mg
Simethicone emulsion	1.6 mg
Purified Water	250 mg

The enteric coating is prepared using the following method:

The talc and titanium dioxide are added to a portion of purified water and mixed until uniform. The triethylcitrate and the simethicone emulsion are added with continuous mixing. The resulting pigment suspension is next passed through a screen or a suitable mill to break up agglomerates. The Eudragit L 30 D-55® is screened and then added to a suitable vessel and diluted with a portion of the purified water. The pigment suspension is then added to the diluted Eudragit suspension and mixed until uniform.

In a suitable coating pan, the compressed tablets (10 kg) containing ibandronate and Citric Acid, described below, are warmed to about 30-35° C. The enteric coating suspension is sprayed onto the tablets at approximately 30 grams per minute. When the spray cycle is completed, the temperature is reduced and the tablets are removed and dried at 30-35° C. for approximately 1 hour.

A coating weight gain of 17% (total solids) is applied by spraying the above composition onto compressed tablets containing Ibandronate and citric acid, prepared in Part B below.

B. Compressed Tablets Containing Ibandronate and Citric Acid

The enteric coating suspension prepared in Part A above is sprayed onto 100 mg Ibandronate tablets, each tablet weighing 600 mg and each containing:

Active Ingredients:	
Ibandronate sodium	100 mg*
Chelant:	
Citric acid	350.0 mg
Excipients:	
Microcrystalline cellulose	132.0 mg
Crospovidone	15.0 mg
Magnesium stearate	3.0 mg

*This amount is calculated on an ibandronic acid basis.

Tablets having the composition set forth above are prepared as follows:

The tablets are prepared by sieving the ibandronate active ingredient and the citric acid with ½ of the microcrystalline cellulose into a twin shell blender. The blend is then mixed until uniform. Then, ½ of the magnesium stearate is added and the blend is mixed further. The blend is then is roller compacted and milled. The remaining microcrystalline cellulose and crospovidone are added and mixed until uniform. The remaining magnesium stearate is then added and mixed until adequate lubrication is achieved. Tablets are then compressed on a rotary tablet press.

Example XII

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Excipients:	
Eudragit S100 ® (dry basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	12.9 mg
Dibutyl Phthalate	2.59
Talc	3.54 mg
Red Iron Oxide	1.37 mg
Isopropyl alcohol	110.7 mg
Acetone	24.74 mg
Purified Water	3.1 mg

The enteric coating is prepared using the following method:

The purified water, approximately 80% of the isopropyl alcohol, and the Eudragit S100 are combined while mixing to form a solution. After mixing for at least 60 minutes, the acetone, dibutyl phthalate, and remaining isopropyl alcohol are added while mixing. Mixing continues through the remainder of the preparation. Ferric oxide and talc are added to the solution and the resulting suspension is then mixed for at least one hour. The coating solution is mixed for at least one hour before production. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 8.5% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 35 mg risedronate tablets, each tablet weighing 240 mg as prepared according to Example IB.

Example XIII

Capsules Containing Enteric-Coated Beads

Capsules containing enteric-coated beads are prepared by preparing enteric-coated beads, and then encapsulating them using a gelatin capsule. The beads consist of inert sugar spheres that are coated with a polymeric film which contains risedronate and EDTA and are prepared using the procedure in Part A below. The beads are next enteric-coated using the procedure described in Part B below.

A. Risedronate- and EDTA-Coated Beads

Component	mg/capsule
Risedronate Sodium	30*
Disodium EDTA	100
Sugar Spheres, 20-25 mesh	115.6
Hydroxypropylmethylcellulose	25
Polyethylene Glycol 3350	2.5
Purified Water	700

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

The risedronate- and EDTA-coated beads are prepared as follows:

The purified water is heated and the hydroxypropylmethylcellulose is slowly added. When the hydroxypropylmethylcellulose is dispersed, the polyethylene glycol is added and the solution is allowed to cool to 30° C. or less. The risedronate and EDTA are then passed through a mill, if needed, to break up any agglomerates, and then mixed with the polymer solution until uniform.

In a suitable coating column, the sugar spheres are warmed to approximately 35° C. and then the risedronate and EDTA coating suspension prepared above is sprayed on by applying a coating 136% weight gain to the beads. When the spray cycle is completed, the air is turned off and the beads are cooled to room temperature.

B. Enteric-Coated Beads

Component	mg/capsule
Risedronate Sodium- and EDTA-coated beads (prepared in Part A above)	273.1
Eudragit L 30 D-55 ® (wet basis)	106
Talc USP	16.9
Triethyl Citrate NF	3.2
Simethicone Emulsion USP	2.1
Yellow Ferric Oxide NF	0.04
Purified Water	225

The talc is added and the yellow ferric oxide is added to a portion of the purified water and mixed until uniform. The triethyl citrate and the simethicone emulsion are added with continued mixing. The resulting pigment suspension is then passed through a screen or a suitable mill to break up agglomerates. The Eudragit L 30 D-55® is screened and then added to a suitable vessel and diluted with a portion of the purified water. The pigment suspension is then added to the diluted Eudragit suspension and mixing is continued.

In a suitable coating column the risedronate- and EDTA-coated beads are warmed to the appropriate temperature. The enteric coating suspension having the composition described in part B is sprayed on the beads. When the spray cycle is completed, the air is turned off. The coated beads are stored at 25-30° C. for a minimum of 12 hours before encapsulating.

The beads are encapsulated utilizing a hard shell gelatin capsule using an appropriate capsule filler.

Example XIV

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Ingredients:

Eudragit L 30 D-55® (wet basis) 47.8 mg

(manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)

Triethylcitrate	2.15 mg
Talc	7.17 mg
Red Iron Oxide	0.07 mg
Simethicone emulsion (30%)	0.14 mg
Polysorbate 80	0.14 mg
Purified Water	102.6 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to the pigment suspension and mixed for at least 45 minutes. The Eudragit L30 D-55® solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated, using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 10% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

The enteric coating suspension prepared in Part A above is sprayed onto 35 mg risedronate tablets, each tablet weighing 240 mg and prepared as in Example IB

Example XV

Enteric-Coated Soft Gelatin Capsules Containing Risedronate and Disodium EDTA

Enteric-coated capsules containing risedronate and EDTA are made by preparing a coating composition and soft gelatin capsules containing risedronate and EDTA, and then applying said coating composition to said soft gelatin capsules.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Excipients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbHand Co. KG, Darmstadt, Germany)	200.0 mg
Dibutyl phthalate	10.0 mg
Talc	30.0 mg
Red Iron Oxide	0.25 mg
Simethicone emulsion (30%)	0.50 mg
Polysorbate 80	0.50 mg
Purified Water	350 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to the pigment suspension and mixed for at least 45 minutes. The Eudragit L 30 D-55 solution and dibutylphthalate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process. The soft gelatin capsules are transferred to the coating pan and preheated with occasional jogging. The soft gelatin capsules are coated, using a typical pan coating process until the required quantity of coating solution has been applied. Capsules are then cooled and collected in suitable containers.

A coating weight gain of 13% (total solids) is applied by spraying the above composition onto soft gelatin capsules containing risedronate and EDTA, prepared in Part B below.

B. Soft Gelating Capsules Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 50 mg risedronate soft gelatin capsules, each weighing 764 mg and each containing:

Fill Composition	
Risedronate sodium	50 mg*
Oleoyl Macrogol-6 Glycerides	370 mg
Colloidal Silicon Dioxide	5 mg
Disodium EDTA	125 mg
Total	550 mg
Gel Shell Composition	
Gelatin	123.4 mg
Glycerin	44.1 mg
Anhydrized Liquid Sorbitol (Sorbitol Special, 76%)	27.1 mg
Purified Water	17.1 mg
Titanium dioxide	1.0 mg
FD&C Red No. 40, E129	0.96 mg
FD&C Blue No. 1, E133	0.30 mg
Total	214 mg
Total Capsule weight	764 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Soft gelatin capsules having the composition set forth above are prepared as follows:

The Oleoyl Macrogol-6 Glycerides is added to a suspension tank equipped with an overhead mixer. The risedronate sodium, disodium EDTA, colloidal silicon dioxide are passed through a mill and added to the Oleoyl Macrogol-6 Glycerides with continued mixing. The mixture is blended for approximately 60 minutes. The blend is then deaerated and ready for filling into capsules. With mixing, the glycerin, sorbitol special, and purified water are combined in a heated vacuum vessel. Heat is applied until the temperature reaches at least 80° C., then the gelatin is added and mixed for 75 minutes. The gel mass is examined for complete dissolution of particles. If needed continue heating and mixing is applied until there is no visual evidence of undissolved particles. The gel mass is deaerated, then the titanium dioxide, FD&C Red No. 40 and FD&C Blue No. 1 are added with continued mixing. The gel mass is discharged into heated gel holding tanks for subsequent processing. The fill material is then encapsulated on a soft gelatin capsule filler.

Example XVI

Enteric-Coated Tablet for Releasing Citric Acid in the Jejunum and Risedronate in the Ascending Colon

An enteric-coated layered tablet containing risedronate sodium in one layer and citric acid in a separate layer is designed so that the citric acid is released in the jejunum and the risedronate is released in the ascending colon. The tablet is prepared according to the following method:

Active layer:

Component	mg/tablet
Risedronate sodium	50 mg*
Hydroxypropylmethylcellulose	100 mg
Starch 1500	90 mg
Microcrystalline Cellulose	50 mg
Stearic Acid	10 mg
Purified water	60 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

A mixture of risedronate sodium, hydroxypropylmethylcellulose, starch 1500, and microcrystalline cellulose is wet granulated in a high shear mixer with purified water. The granulation is then sieved and dried at 30° C. for 12 hours. Then the stearic acid is added and mixed in a low shear mixer until uniform, and the granulation is discharged into a fiber drum.

Citric Acid layer:

Component	mg/tablet
Citric acid	150 mg
Lactose, Hydrous	100 mg
Polyvinylpyrrolidone	10 mg
Microcrystalline Cellulose	50 mg
Stearic Acid	10 mg
Purified water	65 mg

A mixture of citric acid, lactose, polyvinylpyrrolidone and microcrystalline cellulose is wet granulated in a high shear mixer with purified water. The granulation is then sieved and dried at 30° C. for 12 hours. Then the stearic acid is added and mixed in a low shear mixer until uniform then the granulation is discharged into a fiber drum. Tablets are compressed at a weight of 620 mg on a layer tablet press.

The enteric coating has the following composition per tablet:

Component	mg/tablet
Eudragit L100 ®	62
Triethylcitrate	12.5
Isopropyl alcohol	600
Purified water	100

The triethyl citrate is added to the purified water and isopropyl alcohol with continued mixing. The Eudragit L 100® is added with continued mixing. In a suitable coating pan, the compressed layered tablets (10 kg) containing risedronate in one layer and citric acid in a separate layer are warmed to about 30-35° C. The enteric coating suspension is sprayed onto the tablets at approximately 50 grams/minute. When the spray cycle is completed, the temperature is reduced and the tablets are removed and dried at 30-35° C. for approximately 1 hour.

Example XVII

A 65 kg woman diagnosed with postmenopausal osteoporosis is prescribed the enteric-coated oral dosage form of Example 1, to be taken once weekly, comprising 35 mg risedronate and 100 mg Disodium EDTA. The patient takes the oral dosage form with breakfast once per week. A biopsy of iliac crest bone is taken at two years and reveals an increase in mean wall thickness of the remodeling units compared to her baseline biopsy.

Example XVIII

A 70 kg man diagnosed with prostate cancer and high bone turnover is prescribed the enteric-coated oral dosage form of Example 1, to be taken once weekly, comprising 35 mg risedronate and 150 mg citric acid. The patient takes the oral dosage form once per week, immediately before going to sleep. The patient does not experience upper GI irritation or discomfort.

Example XIX

A randomized, open-label, single-dose, single-center, 8-treatment, parallel-group study is performed to compare absorption of oral, fasted immediate release risedronate sodium tablets with fed and fasted risedronate sodium plus EDTA delivered to different locations in the lower GI tract. The study consists of one 72-hour period.

The following treatments are administered to treatment groups A-H:

Treatment Group	Number of Subjects	Dose	Delivery/Status
A	10	35 mg risedronate sodium tablet	Stomach/fasted
B	10	35 mg risedronate sodium + 100 mg disodium EDTA	jejunum/fasted

-continued

Treatment Group	Number of Subjects	Dose	Delivery/Status
C	10	35 mg risedronate sodium + 100 mg disodium EDTA	jejunum/fed
D	10	35 mg risedronate sodium + 100 mg disodium EDTA	terminal ileum/fasted
E	10	35 mg risedronate sodium + 100 mg disodium EDTA	terminal ileum/fed
F	10	35 mg risedronate sodium + 100 mg disodium EDTA	ascending colon/fasted
G	10	35 mg risedronate sodium + 100 mg disodium EDTA	ascending colon/fed
H	10	35 mg risedronate sodium + 100 mg disodium EDTA	descending colon/fasted

For fasted administration, subjects fast overnight and the dose is administered in the morning. Subjects continue to fast until the drug is released at the specified site.

For fed administration (Treatment Groups C, E, and G), subjects are fed a light breakfast and at approximately 3 hours later subjects take the study medication. Immediately following the passing of the study medication from the stomach, these subjects eat a breakfast. Subjects continue to fast until 2 hours after the drug is released at the specified site.

Ratio of Fed to Fasted Urine Recovery for Different Sites of Release

Location of Release	Urinary Recovery (% of dose) Ratio Fed/Fasted
Jejunum	0.959
Ileum	1.131
Ascending Colon	1.560

A ratio near 1 indicates that the absorption is the same with or without food.

Example XX

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate are prepared using a similar method as described in Example I. A coating preparation is prepared as described below.

A. Enteric Coating Suspension

Ingredients:	
Eudragit FS30D (wet basis)	57.6 mg
Eudragit FS30D (dry basis)	17.3 mg
Triethylcitrate	0.86 mg
Talc	5.18 mg
Red iron oxide	0.07 mg
Simethicone emulsion (30%)	0.21 mg
Polysorbate 80	0.55 mg
Purified water	160.1 mg

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to the pigment suspension and mixed for at least 45 minutes. The Eudragit FS30D solution and triethylcitrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process.

The compressed risedronate tablets as described in Example I are transferred to the coating pan and preheated with occasional jogging. The compressed tablets are coated with the Enteric-Coating Suspension using a typical pan process until the required coating has been applied.

All documents cited are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

What is claimed is:

1. An oral dosage form having pharmaceutically effective absorption comprising:
   (a) from about 1 mg to about 500 mg of a bisphosphonate which is selected from the group consisting of risedronate and acids, salts, and esters thereof;
   (b) from about 10 mg to about 500 mg of EDTA; and
   (c) a delayed release mechanism to deliver the bisphosphonate and the EDTA in the lower gastrointestinal tract.

2. The oral dosage form of claim 1 wherein the EDTA is disodium EDTA.

3. The oral dosage form of claim 1 wherein the delayed release mechanism is selected from the group consisting of *pH triggered delivery systems, bacterial enzyme triggered* delivery systems, time dependent delivery systems and combinations thereof.

4. The oral dosage form of claim 3 wherein the delayed release mechanism is a pH triggered delivery system.

5. The oral dosage form of claim 4 wherein the pH triggered delivery system comprises an enteric coating.

6. The oral dosage form of claim 1 comprising from about 10 mg to about 200 mg of risedronate sodium.

7. The oral dosage form of claim 6 comprising from about 75 mg to about 250 mg of the EDTA, wherein the EDTA is disodium EDTA.

8. An oral dosage form having pharmaceutically effective absorption comprising:
   (a) from about 1 mg to about 500 mg of risedronate sodium;
   (b) from about 75 mg to about 250 mg of disodium EDTA; and
   (c) an enteric coating which provides for release of the risedronate sodium and the disodium EDTA in the lower gastrointestinal tract of a mammal.

9. A method for treating a disease selected from the group consisting of osteoporosis, Paget's disease, hyperparathyroidism, hypercalcemia of malignancy, osteolytic bone metastasis, and combinations thereof, comprising administering to a human or other mammal in need thereof a safe and effective amount of the oral dosage form of claim 8.

10. The method of claim 9 wherein the disease is osteoporosis.

11. The method of claim 9 wherein the oral dosage form is administered according to a continuous schedule having a

dosing interval selected from the group consisting of daily, weekly, three times per month, twice monthly, and once monthly.

12. The method of claim **11** wherein the oral dosage form is administered weekly.

13. The oral dosage form of claim **8** comprising from about 10 mg to about 50 mg of risedronate sodium.

14. The oral dosage form of claim **13** comprising about 100 mg of the disodium EDTA.

15. The oral dosage form of claim **14** comprising about 35 mg of risedronate sodium.

16. The oral dosage form of claim **15** wherein the enteric coating is a methacrylic acid copolymer.

17. The oral dosage form of claim **8** comprising from about 50 mg to about 200 mg of risedronate sodium.

18. The oral dosage form of claim **17** comprising about 100 mg of the disodium EDTA.

19. The oral dosage form of claim **18** comprising about 150 mg of risedronate sodium.

20. The oral dosage form of claim **19** wherein the enteric coating is a methacrylic acid copolymer.

21. A method for treating osteoporosis comprising administering to a human or other mammal in need thereof a safe and effective amount of the oral dosage form of claim **15**.

22. The method of claim **21** wherein the oral dosage form is administered with or without food.

23. A method for treating osteoporosis comprising administering to a human or other mammal in need thereof a safe and effective amount of the oral dosage form of claim **19**.

24. The method of claim **23** wherein the oral dosage form is administered with or without food.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,645,459 B2
APPLICATION NO. : 11/106816
DATED : January 12, 2010
INVENTOR(S) : Richard John Dansereau

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1215 days.

Signed and Sealed this

Twelfth Day of October, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,645,459 B2
APPLICATION NO. : 11/106816
DATED : January 12, 2010
INVENTOR(S) : Richard John Dansereau et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

ON THE TITLE PAGE [56] REFERENCES CITED:

Foreign Patent Documents, "809120 A2" should read --8091202 A2--.

ON THE TITLE PAGE [75] INVENTORS:

Inventors, "Richard John Dansereau, Cilncinnati, OH (US);" should read
--Richard John Dansereau, Cincinnati, OH (US);--.

COLUMN 2:

Line 52, "it was" should read --it is--.

COLUMN 3:

Line 6, "instruct" should read --instructs--; and
Line 8, "are instructed" should read --instructs them--.

COLUMN 4:

Line 22, "active" should read --active ingredient--.

COLUMN 5:

Line 15, "active" should read --active ingredient--.

COLUMN 6:

Line 54, "Alendronate." should read --alendronate.--.

Signed and Sealed this
Twenty-eighth Day of December, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)
U.S. Pat. No. 7,645,459 B2

COLUMN 9:

Line 2, "precipitate" should read --precipitates--.

COLUMN 10:

Line 50, "primary" should read --primarily--.

COLUMN 12:

Line 32, "copolymer" should read --copolymers--;
Line 36, "is" should read --are--; and
Line 47, "an" should be deleted.

COLUMN 13:

Line 35, "poly(methyacrylic acid," should read --poly(methacrylic acid,--; and
Line 40, "trimellatate," should read --trimellitate,--.

COLUMN 14:

Line 44, "secabate" should read --sebacate--; and
Line 49, "herein above." should read --hereinabove.--.

COLUMN 15:

Line 65, "L-100®" should read --L-100®,--; and
Line 66, "F530D®" should read --F530D®,--.

COLUMN 16:

Line 6, "CO.," should read --Co.,--; and
Line 23, "saccharide" should read --saccharide(s)--.

COLUMN 18:

Line 36, "active" should read --active ingredient--.

COLUMN 19:

Line 54, "Eudragit L 30 D-55" should read --Eudragit L 30 D-55®--; and
Line 57, "Eudragit" should read --Eudragit®--.

CERTIFICATE OF CORRECTION (continued)
U.S. Pat. No. 7,645,459 B2

COLUMN 21:

Line 58, "Macrocrystalline cellulose" should read --Microcrystalline cellulose--.

COLUMN 24:

Line 26, "Röhm Pharma Gmbhand Co." should read --Röhm Pharma GmbH and Co.--;
Line 36, "Eudragit E 100" should read --Eudragit E 100®--;
Line 37, "B" should be deleted and "hydroxyproylmethylcelluse" should read --hydroxypropylmethylcellulose--;
Line 38, "mix" should read --mixed--;
Line 48, "Röhm Pharma Gmbhand Co." should read --Röhm Pharma GmbH and Co.--; and
Line 57, "oxide," should read --oxide--.

COLUMN 25:

Line 63, "Dibuty Sebacate" should read --Dibutyl Sebacate--; and
Line 64, "Ethyl Alcholc" should read --Ethyl Alcohol--.

COLUMN 26:

Line 6, "dibuty sebacate" should read --dibutyl sebacate--;
Line 15, "Röhm Pharma GmbHand Co." should read --Röhm Pharma GmbH and Co.--;
Line 25, "oxide," should read --oxide--;
Line 27, "Eudragit L 30D 55" should read --Eudragit L 30D-55®--;
Line 29, "Eudragit" should read --Eudragit®--; and
Line 40, "13% Enteric" should read --13% for the Enteric--.

COLUMN 28:

Line 4, "Spray" should read --spray--;
Line 24, "aledronate, each tablet weighing" should read --aledronate tablets each weigh--;
Line 25, "containing:" should read --contain:--;
Line 40, "a" should read --an--; and
Line 54, "coating" should read --coated--.

COLUMN 31:

Line 7, "is roller" should read --roller--;
Line 32, "Dibutyl Phthalate 2.59" should read --Dibutyl Phthalate 2.59 mg--; and
Line 42, "Eudragit S100" should read --Eudragit S100®--.

COLUMN 32:

Line 60, "Eudragit" should read --Eudragit®--.

CERTIFICATE OF CORRECTION (continued)
U.S. Pat. No. 7,645,459 B2

COLUMN 33:

Lines 18-21 should be deleted;
Line 25, "Triethylcitrate 2.15 mg" should read

Ingredients:	
Eudragit L 30 D-55® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	47.8 mg
Triethylcitrate	2.15 mg

--; and

Line 42, "Eudragit" should read --Eudragit®--.

COLUMN 34:

Line 9, "Röhm Pharma Gmbhand Co." should read --Röhm Pharma GmbH and Co.--;
Line 25, "Eudragit L 30 D-55" should read --Eudragit L 30 D-55®--;
Line 28, "Eudragit" should read --Eudragit®--; and
Line 39, "Gelating" should read --Gelatin--.

COLUMN 37:

Line 55, "Eudragit FS30D (wet basis) 57.6 mg" should read --Eudragit FS30D® (wet basis) 57.6 mg--; and
Line 56, "Eudragit FS30D (dry basis) 17.3 mg" should read --Eudragit FS30D® (dry basis) 17.3 mg--.

COLUMN 38:

Line 1, "Eudragit FS30D" should read --Eudragit FS30D®--; and
Line 4, "Eudragit" should read --Eudragit®--.

U 7346838

THE UNITED STATES OF AMERICA

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U.S. PATENT: *7,645,460*
ISSUE DATE: *January 12, 2010*

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WC v. Amneal, Teva, Ranbaxy (DNJ 11-5989, 11-6936, 12-2474)
DTX-0003

DX 3
4-11-13


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Dansereau et al.

(10) **Patent No.: US 7,645,460 B2**
(45) **Date of Patent: *Jan. 12, 2010**

(54) **DOSAGE FORMS OF RISEDRONATE**

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(73) Assignee: **The Procter & Gamble Company**, Cincinnati, OH (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 613 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/286,875**

(22) Filed: **Nov. 23, 2005**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 11/106,816, filed on Apr. 15, 2005.

(60) Provisional application No. 60/573,881, filed on May 24, 2004.

(51) **Int. Cl.**
A61K 9/28 (2006.01)
A61K 9/20 (2006.01)
A61K 31/675 (2006.01)

(52) **U.S. Cl.** **424/474**; 424/465; 424/468; 514/89

(58) **Field of Classification Search** 424/474
See application file for complete search history.

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(74) *Attorney, Agent, or Firm*—Kelly L. McDow; Mary Pat McMahon

(57) **ABSTRACT**

Oral dosage forms of a risedronate comprised of a safe and effective amount of a pharmaceutical composition comprising risedronate, a chelating agent, and, means for effecting delayed release of the risedronate and the chelating agent in the small intestine provide immediate release of the pharmaceutical composition to the small intestine of the mammal subject and pharmaceutically effective absorption of the bisphosphonate with or without food or beverages. The present invention substantially alleviates the interaction between risedronate and food or beverages, which interaction results in the bisphosphonate active ingredient not being available for absorption. The resulting oral dosage form may thus be taken with or without food. Further, the present invention effects delivery of risedronate and the chelating agent to the small intestine, substantially alleviating the upper GI irritation associated with bisphosphonate therapies. These benefits simplify previously complex treatment regimens and can lead to increased patient compliance with bisphosphonate therapies.

30 Claims, No Drawings

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DOSAGE FORMS OF RISEDRONATE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. application Ser. No. 11/106,816, filed Apr. 15, 2005 which claims the benefit of Provisional Application Ser. No. 60/573,881, May 24, 2004

FIELD OF THE INVENTION

The present invention relates to oral dosage forms of risedronate comprised of a safe and effective amount of a pharmaceutical composition comprising a bisphosphonate, a chelating agent for enabling administration of risedronate with food or beverages, means for effecting delayed release of risedronate and the chelating agent in the small intestine, and one or more pharmaceutically-acceptable excipients. The oral dosage forms of the invention provide delivery of the pharmaceutical composition to the small intestine of the mammal subject and provide pharmaceutically effective absorption of risedronate when administered with or without food or beverages. The present invention further relates to a method of treating or preventing diseases characterized by abnormal calcium and phosphate metabolism comprising administering to a human or other mammal in need thereof the oral dosage form described herein.

BACKGROUND OF THE INVENTION

Bisphosphonates were first developed to complex calcium in hard water to improve detergent performance. Bisphosphonates have since been found to be useful in the treatment and prevention of diseases or conditions characterized by abnormal calcium and phosphate metabolism. Such conditions may be divided into two broad categories:

1. Conditions which are characterized by anomalous mobilization of calcium and phosphate leading to general or specific bone loss or excessively high calcium and phosphate levels in the fluids of the body. Such conditions are sometimes referred to herein as pathological hard tissue demineralization.

2. Conditions which cause or result from deposition of calcium and phosphate anomalously in the body. These conditions are sometimes referred to herein as pathological calcifications.

The first category includes osteoporosis, a condition in which bone hard tissue is lost disproportionately to the development of new hard tissue. Essential quantities of cancellous bone are lost, and marrow and bone spaces become larger, resulting in reduced cancellous bone strength. Bone also becomes less dense and fragile. Osteoporosis can be subclassified as senile, drug induced (e.g., adrenocorticoid, as can occur in steroid therapy), disease induced (e.g., arthritic and tumor), etc., however the manifestations are similar. Another condition in the first category is Paget's disease (osteitis deformans). In this disease, dissolution of normal bone occurs, which is then haphazardly replaced by soft, poorly mineralized tissue such that the bone becomes deformed from pressures of weight bearing, particularly in the tibia and femur. Hyperparathyroidism, hypercalcemia of malignancy, and osteolytic bone metastasis are conditions also included in the first category.

The second category, involving conditions manifested by anomalous calcium and phosphate deposition, includes myositis ossificans progressiva, calcinosis universalis, and such

afflictions as arthritis, neuritis, bursitis, tendonitis, and other inflammatory conditions which predispose involved tissue to deposition of calcium phosphates.

Bisphosphonates tend to inhibit the resorption of bone tissue, which is beneficial to patients suffering from excessive bone loss. However, many of the early bisphosphonates, such as ethane-1,1-diphosphonic acid (EHDP), propane-3-amino-1-hydroxy-1,1-diphosphonic acid (APD), and dichloromethane diphosphonic acid (Cl_2MDP), have the propensity of inhibiting bone mineralization when administered at high dosage levels. Although more biologically potent bisphosphonates exist, which can be administered at lower dosage levels (such as 1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate), alendronate, ibandronate, and zoledronate), oral administration of bisphosphonates sometimes results in patient complaints shortly after dosing. These complaints are usually characterized by the patients as heartburn, esophageal burning, pain and/or difficulty upon swallowing, and/or pain existing behind and/or mid-sternum. It is hypothesized that this irritation results from the bisphosphonate tablet adhering to epithelial and mucosal tissues, resulting in the topical irritation thereof. In order to avoid potential upper gastrointestinal irritation, patients taking bisphosphonates are instructed to take their medication with a full glass of water, and to remain upright for at least thirty minutes after taking an oral dose of a bisphosphonate.

It is known that oral doses of bisphosphonates are poorly absorbed (less than 1% of the oral dose) in the gastrointestinal (GI) tract. See Ezra et al., Adv. Drug Del. Rev. 42: 175-95 (2000). Several approaches have been suggested for increasing absorption of oral bisphosphonates throughout the GI tract. These approaches include modifying the permeability properties of the intestinal mucosa (e.g., through the use of absorption enhancers), or altering the physical or chemical properties of the bisphosphonate compounds themselves (e.g., through prodrugs).

While the use of absorption enhancers, such as ethylenediaminetetraacetic acid (EDTA), that increase intestinal permeability at high doses, has been proposed as a means of increasing absorption of oral bisphosphonates, the applicability of EDTA as an agent in human pharmacotherapy has been thought to be "impossible" in light of the effects of EDTA on mucosal integrity. Ezra et al., Adv. Drug Del. Rev. 42: 185 (2000). Still others have concluded that the high amount of EDTA required to effect an increase in GI absorption would exclude the agent as a candidate for use in oral bisphosphonate therapies. See Janner et al., Calcif. Tissue Int. 49: 280-83 (1991).

While the primary site of bisphosphonate absorption is the small intestine, bisphosphonates such as risedronate have similar absorption throughout the small intestine independent of where it was delivered. See Mitchell et al., Pharm Res., Vol. 15, No. 2: 228-232 (1998). Thus targeted delivery of the bisphosphonate alone to the small intestine would not increase absorption or efficacy of the bisphosphonate. However, others have attempted to increase the absorption of bisphosphonates by increasing the permeability of the intestinal mucosa through delivery of microparticles of chelating agents and bisphosphonate to the reported site of absorption (BR2001-006601).

Bisphosphonates such as risedronate and alendronate have been approved by a number of regulatory agencies as being effective in the treatment of various bone pathologies. However, interactions between bisphosphonates and foods and minerals (especially cations like calcium, magnesium, aluminum, and iron-containing foods or supplements) cause less of the bisphosphonate to be available for absorption. For

example, in Mitchell et. al., Br. J. Clin. Pharmacol. 48: 536-542 (1999), it was demonstrated that administration of risedronate within 30 minutes of a meal reduced the amount absorbed by 50% compared to administration in the fasting state. In order to reduce this food effect, the labeling of oral bisphosphonate products instruct patients to take their medication at least thirty minutes or in the case of Ibandronate sixty minutes, before the first food of the day, and are instructed to take their calcium supplements at another time of the day, or on a day when they are not taking an oral dose of a bisphosphonate. These dosing instructions can seem complex and inconvenient to the patient, which can lead to poor patient compliance.

There is an ongoing need to develop an oral dosage form of a bisphosphonate which can be taken with or without food or beverages (i.e. has pharmaceutically effective absorption regardless of food or beverage intake), at the preference of the patient, and which does not produce upper gastrointestinal irritation.

It has been found that a pharmaceutical composition comprising risedronate, a sufficient amount of chelating agent to bind the ions and minerals in food, and a means for effecting delayed release of risedronate and the chelating agent in the small intestine is useful in providing an oral dosage form which provides immediate release of risedronate to the small intestine, as well as pharmaceutically effective absorption of risedronate when administered with or without food or beverages. The oral dosage forms of the present invention may be taken with or without food or beverages, thus simplifying the bisphosphonate treatment therapy and leading to increased patient compliance and convenience. Further, the oral dosage forms of the invention provide for delayed release of risedronate and the chelating agent in the small intestine, which may alleviate the upper gastrointestinal irritation experienced with other oral bisphosphonate dosage forms and the need to remain upright for thirty minutes post-dose administration.

SUMMARY OF THE INVENTION

The present invention relates to an oral dosage form of risedronate active ingredient comprising a safe and effective amount of a pharmaceutical composition comprising:

(a) from about 1 mg to about 250 mg risedronate;

(b) from about 10 mg to about 970 mg of a chelating agent; and

(c) a delayed release mechanism to immediately release the risedronate and the chelating agent in the small intestine; wherein such composition is a tablet size of no greater than one gram.

The dosage forms of the present invention provide an immediate release of risedronate and the chelating agent to the small intestine of the mammal subject and pharmaceutically effective absorption of risedronate active ingredient when administered with or without food or beverages.

The present invention substantially alleviates the interaction between risedronate and food, which interaction results in decreased absorption of risedronate. The resulting novel oral dosage form may thus be taken with or without food or beverages, which simplifies previously complex treatment regimens and can lead to increased patient compliance with bisphosphonate therapies and if the patients are compliant their disease can be better treated. The invention further alleviates the potential for upper gastrointestinal irritation associated with non-delayed, immediate release oral dosage forms of bisphosphonates, by delaying release of the bisphosphonate active ingredient until the bisphosphonate and the chelating agent reach the small intestine.

The present invention further relates to a method of treating or preventing diseases characterized by abnormal calcium and phosphate metabolism comprising administering to a human or other mammal in need thereof the oral dosage form described herein.

The invention further relates to a kit comprising one or more oral dosage forms of the present invention and means for facilitating compliance with methods of this invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Usage of Terms

The term "immediate release" as used herein means dissolution of the core tablet in less than 60 minutes, when measured by standard USP definitions. For example, the USP specifies that all tablets and capsules are subject, to a general dissolution standard of not less than 75% of the core content is dissolved in not more than 45 minutes in 900 mL of water, using the apparatus, procedures, and interpretation presented in the United States Pharmacopeia chapter, Dissolution, page 959. For this purpose, 75% is Q, and conformance is demonstrated with either one of Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm."

The terms "continuous" or "continuously," as used herein, mean at regular specified intervals. For example, a continuous schedule according to a dosing regimen of once weekly means that the active is given one time per week for an unspecified period of time or for as long as treatment is necessary.

The term "delayed release or delayed delivery," as used herein, refers to formulating the pharmaceutical composition comprising risedronate and the chelating agent so that their release will be accomplished at some generally predictable location in the small intestine.

The term "nutrient," as used herein, means any nutritional or dietary supplement including but not limited to vitamins, minerals, amino acids, herbs or other botanicals, or concentrates, metabolites, constituents, extracts, or combinations of the same.

The term "pharmaceutical composition," as used herein, means an oral dosage form comprised of a safe and effective amount of risedronate and one or more pharmaceutically-acceptable excipients including at least one chelating agent. The pharmaceutical compositions described herein are comprised of from 0.5% to 75%, preferably from 1% to 40% of risedronate and from 25% to 99.5%, preferably from 60% to 99% of pharmaceutically-acceptable excipients including at least one chelating agent.

The term "safe and effective amount," as used herein, means an amount of a compound or composition high enough to significantly positively modify the symptoms and/or condition to be treated, but low enough to avoid serious side effects (at a reasonable risk/benefit ratio), within the scope of sound medical judgment. The safe and effective amount of active ingredient for use in the method of the invention herein will vary with the particular condition being treated, the age and physical condition of the patient to be treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient being employed, the particular pharmaceutically-acceptable excipients utilized, and like factors within the knowledge and expertise of the attending physician.

The term "pharmaceutically effective absorption" as used herein means an amount of a chelating compound high enough to significantly bind the metal ions and minerals in food but low enough not to significantly alter absorption of

risedronate as compared to absorption in the fasted state. That is, absorption is similar with or without food. Given the high variability of bisphosphonate absorption, fed exposure within about 50% of fasting exposure is expected to be pharmaceutically effective absorption.

The term "oral dosage form," as used herein, means any pharmaceutical composition intended to be delivered or released to the small intestine of a human or other mammal via the mouth of said human or other mammal. For the purposes of the present invention, the delivered form can be in the form of a compressed tablet containing granules or particles of risedronate and a chelating agent

The term "unit dose" or "unit dosage" means a dosage form containing an amount of pharmaceutical active or nutrient suitable for administration in one single dose, according to sound medical practice. The present invention is particularly useful for the administration of unit doses in the form of tablets and capsules.

The term "gastrointestinal tract" or "GI tract," as used herein, relates to the alimentary canal, i.e., the musculomembranous tube about thirty feet in length, extending from the mouth to the anus. The term "upper gastrointestinal tract," as used herein, means the buccal cavity, the pharynx, the esophagus, and the stomach. The term "lower gastrointestinal tract," as used herein, means the small intestine and the large intestine.

The term "small intestine," as used herein, means the part of the small intestine consisting of just distal to the stomach, including the duodenum, the jejunum, and the ileum, i.e., that portion of the intestinal tract just distal to the duodenal sphincter of the fundus of the stomach and proximal to the large intestine. The term "large intestine," as used herein, means the part of the lower gastrointestinal tract including the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum

Risedronate

The terms "bisphosphonate" and "diphosphonate," as used herein, include acids, salts, esters, hydrates, polymorphs, hemihydrates, solvates, and derivatives thereof. The bisphosphonates of the present invention include those forms of 1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate) as described in U.S. Pat. No. 5,583,122, to Benedict et al., issued Dec. 10, 1996; U.S. Pat. No. 6,410,520 B2, to Cazer et al., issued Jun. 25, 2002

Non-limiting examples of salts useful herein include those selected from the group consisting of alkali metal, alkaline metal, ammonium, and mono-, di-, tri-, or tetra-C_1-C_{30}-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, and ammonium salts.

The amount of risedronate contained in the oral dosage forms of the present invention will depend on the particular risedronate form selected and the continuous dosing schedule upon which the risedronate is dosed to the patient. Continuous dosing schedules of daily, weekly, twice monthly, three times per month, and once monthly are non-limiting examples of dosing regimens suitable for use with the oral dosage forms of the present invention. The terms "three times per month" or "thrice monthly" mean that an oral dosage form is administered thrice, i.e., three times, during a monthly calendar period. In a thrice monthly schedule, the oral dosage forms may be administered on three consecutive days, or once about every nine to eleven days. The terms "twice per month" or "twice monthly" mean that an oral dosage form is administered twice, i.e., two times, during a monthly calendar period. In a twice monthly regimen, the oral dosage forms may be administered on consecutive days or once about every fourteen to sixteen days. The terms "monthly" or "once monthly" mean that an oral dosage form is administered once, i.e., one time during a monthly calendar period, that is, about every 28 to 31 days.

Mixed nomenclature is currently in use by those of ordinary skill in the art, for example reference to a specific weight or percentage of a bisphosphonate active ingredient is on an anhydrous monosodium salt basis for risedronate. For the present invention, the phrase "about 35 mg of risedronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an anhydrous monosodium salt basis" means that the amount of the risedronate compound selected is calculated based on about 35 mg of anhydrous risedronate monosodium salt.

Generally, the oral dosage forms of the present invention will contain from about 1 mg to about 250 mg of risedronate on a risedronate anhydrous monosodium salt basis. A daily oral dosage form of the present invention contains from about 1 mg to about 10 mg risedronate on a risedronate anhydrous monosodium salt basis. A weekly oral dosage form contains from about 10 to about 70 mg risedronate on a risedronate anhydrous monosodium salt basis, preferably from 15 to about 55 mg risedronate, more preferably from about 35 mg to about 50 mg risedronate. A twice monthly oral dosage form contains from about 20 to about 120 mg risedronate, preferably about 75 mg to about 90 mg risedronate on a risedronate anhydrous monosodium salt basis. An oral dosage form that is administered three times per month contains from about 15 to about 90 mg risedronate, preferably about 50 mg to about 75 mg risedronate, on a risedronate anhydrous monosodium salt basis. A monthly oral dosage form contains from about 50 to about 280 mg risedronate, preferably from about 100 to about 250 mg risedronate, and more preferably about 150 to about 200 mg risedronate on a risedronate anhydrous monosodium salt basis. In one embodiment of the invention the dosage form contains about 100% of the effective amount of the risedronate as equivalent non-chelating agent containing, non-delayed, immediate released risedronate tablets. In yet another embodiment of the invention the dosage form is about 145% of the effective amount of the risedronate as equivalent non-chelating agent containing, non-delayed, immediate released risedronate tablets.

Chelating Agent

The term "chelating agent," as used herein, means a molecule containing two or more electron donor atoms that can form coordinate bonds to a single metal ion. The term "chelating agent" is understood to include the chelating agent as well as salts thereof. For example, the term "chelating agent" includes citric acid as well as its salt forms.

The most common and widely used chelating agents coordinate to metal atoms through oxygen or nitrogen donor atoms, or both. Other less common chelating agents coordinate through sulfur in the form of —SH (thiol or mercapto) groups. After the first coordinate bond is formed, each successive donor atom that binds creates a ring containing the metal atom. A chelating agent may be bidentate, tridentate, tetradentate, etc., depending upon whether it contains two, three, four, or more donor atoms capable of binding to the metal atom. See Kirk-Othmer Encyclopedia of Chemical Technology (4th ed. 2001).

In homogeneous dilute solutions, the equilibrium constant for the formation of the complex from the solvated metal ion (e.g., calcium) and the chelating agent in its fully dissociated form is called the formation or stability constant, K. The practical significance of formation constants is that a high log

K value means a large ratio of chelated to unchelated (or free) metal ion, when equivalent amounts of metal ion and chelating agent are present. Higher ratios (or difference if K is expressed in log units) of the chelating agent and the bisphosphonate complexation constants are preferred in order to have nearly all of the metal ion complexed to the chelating agent instead of the bisphosphonate. For example, for equal molar amounts of both bisphosphonate and the chelating agent, in order for the metal ions to be 99% complexed to the chelating agent, the chelating agent must have a log K which is at least 4 units higher than the bisphosphonate-metal ion complex. The other technique which can be used to favor the chelating agent-metal ion complex over that of the bisphosphonate-metal ion complex is to add a molar excess of the chelating agent which relies on the law of mass action to favor formation of the chelating agent-metal ion complex.

Although pH and solution concentration can affect the formation constant, in general, the log K of the chelating agent is preferably at least equal to that of the bisphosphonate. In other instances the log K of the chelating agent is 2 to 5 units higher than that of the bisphosphonate. In other instances, the chelating agent is present at a molar excess to that of the bisphosphonate. The chelating agent in such instances is present in at least a 2:1 molar ratio of the chelating agent to bisphosphonate.

The chelating agent and the form it is administered is at least 50% as soluble in water as risedronate. In other instances the chelating agent and the form it is administered may have a solubility comparable to or greater than that of risedronate.

In one embodiment, the chelating agent is selected from the group consisting of sodium or disodium EDTA, citric acid, malic acid, tartaric acid, lactic acid, adipic acid, succinic acid, lysine, sodium hexametaphosphate, and combinations thereof. In another embodiment, the chelating agent is sodium of disodium EDTA, citric acid, or sodium hexametaphosphate.

The amount of chelating agent present in the oral dosage form of the present invention will depend on the particular chelating agent or agents (i.e. mixtures of chelating agents) selected, the amount of bisphosphonate active ingredient present in the oral dosage form, and the specific portion of the small intestine where delivery and release of the chelating agent and/or bisphosphonate active ingredient is desired. After the ingestion of milk, it has been shown in the art that the concentration of calcium decreases over the length of the lower GI tract, beginning with the small intestine and proceeding through to the end of the small intestine. Mahe, J. et al., *Gastroileal nitrogen and electrolyte movements after bovine milk ingestion in humans*, Am. J. Clin. Nutr. 56: 410-16 (1992).

The concentration of calcium in the stomach is approximately 10-fold higher than that of the concentration in the jejunum and approximately 40 times that in the ileum. Thus, if the risedronate and chelating agent were released in the stomach (with food), the amount of chelating agent of the present invention would be insufficient to overcome the effect of calcium on drug absorption. The concentration of calcium in the jejunum and ileum are lower and by targeting release of the dosage form in these regions where the amount of calcium is lower, the chelating agent is more effective at binding most of all of the calcium than if released in the stomach. It is also desirable not only to have targeted release of the tablet in the small intestine but after the coating dissolves the chelating agent and risedronate from the core tablet releases in an immediate release fashion. This maximizes the local concentration of the chelating agent in relationship to that of the calcium in the small intestine. Slow or prolonged delivery of the chelating agent in the small intestine does not achieve the desired local concentration of the chelating agent and this type of delivery will not overcome the food effect.

Generally, the oral dosage forms of the present invention will contain a safe and effective amount of a chelating agent suitable for achieving the desired chelating effect, that is, chelating the residual metal ions that are present in the gastrointestinal tract from food at the site of delivery without significantly affecting the absorption of the bisphosphonate had no food been present. In one embodiment, the oral dosage form contains from about 10 mg to about 1000 mg of a chelating agent per unit dose. In another embodiment, the oral dosage forms contain from about 10 mg to about 500 mg of a chelating agent per unit dose. When the chelating agent is disodium EDTA, the preferred range is from about 55 mg to about 500 mg, preferably from about 75 mg to about 250 mg per unit dose. When the chelating agent is citric acid, the preferred range is from about 100 mg to about 970 mg, preferably from about 250 mg to about 500 mg per unit dose.

Delayed Delivery to the Small Intestine

The ultimate site of and/or the rate of delivery in the small intestine can be satisfactorily controlled by one skilled in the art, by manipulating any one or more of the following:

(a) the active ingredient proper;

(b) the type and level of disintegrant;

(c) the type of coating, the type and level of excipients added to the coating and the concomitant desirable thickness and permeability (swelling properties) of the coating;

(d) the time dependent conditions of the coating itself and/or within the coated tablet, particle, bead, or granule;

(e) the particle size of the granulated active ingredient;

(f) the pH dependent conditions of the coating itself and/or within the coated tablet, particle, bead, or granule;

(g) the particle size or solubility of the chelating agent;

(h) the dissolution rate of the coating;

(i) size or shape of the tablet.

In addition the pharmacodynamic effect of the tablets, after multiple dosing, should be within at least 75% of the comparable immediate release tablet.

Delayed Release in the Small Intestine

A human or other mammal suffering from diseases or disorders involving calcium and phosphate metabolism can be successfully treated by the delivery of risedronate to the small intestine of said human or other mammal. The novel dosage forms described herein effect an immediate release to the small intestine, and prohibit the undesired release of risedronate in the mouth, pharynx, esophagus, and/or stomach, thereby prohibiting the erosion, ulceration, or other like irritation of the epithelial or mucosal layers of these tissues.

The chelant and risedronate are released rapidly and as close to simultaneously as possible. This causes the local concentration of chelating agent to be higher in relationship to the metal ions in the food. The higher local concentration of chelating agent in the environment where the active is released may more effectively complex the metals in the food and facilitate absorption of the bisphosphonate. This can be conveniently achieved from a single tablet.

Various means for targeting release of risedronate and the chelating agent in the small intestine are suitable for use in the present invention. Non-limiting examples of means for delivery to the small intestine include pH triggered delivery systems and time dependent delivery systems.

pH Triggered Delivery Systems

One embodiment of the present invention involves coating (or otherwise encapsulating) the risedronate and the chelating agent(s) with a substance which is not broken down, by the gastrointestinal fluids to release the risedronate and the chelating agent until a specific desired point in the intestinal tract is reached. In one embodiment, delayed release of the pharmaceutical composition is achieved by coating the tablet, capsule, particles, or granules, of the risedronate and the chelating agent with a substance which is pH dependent, i.e., broken down or dissolves at a pH which is generally present in the small intestine, but not present in the upper GI tract (i.e., the mouth, buccal cavity, pharynx, esophagus, or stomach) or lower GI tract.

In some cases, it may be desirable that the risedronate and the chelating agent are released at a particular location in the small intestine. In other cases, it may be desirable to release the risedronate and the chelating agent independently at different locations within the small intestine. For example, it may be desirable to release the chelating agent in the, jenunum and the risedronate in the ileum When targeted release of the risedronate and the chelating agent together or separately in particular locations within the small intestine is desired, the selection of the coating material and/or the method of coating or otherwise combining the risedronate and the chelating agent with the selected coating material or other pharmaceutically-acceptable excipients may be varied or altered as is described herein, or by any method known to one skilled in the art.

Solubility, acidity, and susceptibility to hydrolysis of the different risedronate active ingredients, such as acid addition salts, salts formed with the phosphonic group (e.g., alkali metal salts, alkaline earth metal salts, etc.), and esters (e.g., alkyl, alkenyl, aryl, arylalkyl) may be used as guidelines for the proper choice of coating. In addition, suitable pH conditions might be established within the coated tablets, particles, or granules by adding a suitable buffer to the active ingredient in accordance with the desired release pattern.

One embodiment of the present invention is delivered to the small intestine utilizing a pH dependent enteric coating material made from a partly methyl esterified methacrylic acid polymer. The oral dosage form can be in the form of an enteric coated compressed tablet made of granules or particles of active ingredient.

Any enteric coating which is insoluble at a pH below 5.5 (i.e., that generally found in the mouth, pharynx, esophagus, and stomach), but soluble between about pH 5.5 and about pH 6.5 (i.e., that present in the small intestine) can be used in the practice of the present invention. Accordingly, when it is desired to effect delivery of the bisphosphonate and the chelating agent to the small intestine, any enteric coating is suitable which is wholly- or partially-insoluble at a pH below 5.5 and soluble at about a pH 5.5 to about pH 6.5.

The enteric coating must be applied to the compressed tablet, or capsule (e.g., gelatin, starch, or hydroxypropylmethylcellulose) in a sufficient thickness so that the entire coating does not dissolve in gastrointestinal fluids at a pH below 5.5, but does dissolve at a pH above about 5.5 and below pH about 6.5. The dissolution or disintegration of the excipient coating generally does not occur until the entry of the coated dosage form into the small intestine.

It is expected that any anionic polymer exhibiting the requisite pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery of the bisphosphonate and chelating agent to the small intestine. The coating chosen must be compatible with the particular risedronate active ingredient selected. The preferred polymers for use in the present invention are anionic carboxylic polymers. It is particularly preferred that the polymers are acrylic polymers, more preferably partly methyl-esterified methacrylic acid polymers, in which the ratio of free anionic carboxyl groups to ester groups is about 1:1

A particularly suitable methacrylic acid copolymer is Eudragit L®, particularly Eudragit L 30 D-55® and Eudragit L 100-55®, manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany. In Eudragit L 30 D-55®, the ratio of free carboxyl groups to ester groups is approximately 1:1. Further, said copolymer is known to be insoluble in GI fluids having a pH below 5.5, generally 1.5-5.5, i.e., that generally present in the fluid of the upper GI tract, but readily soluble at pH above 5.5, i.e., that generally present in the fluid of the small intestine.

The coating can, and usually will, contain a plasticizer and possibly other coating excipients such as coloring agents, surfactant, talc, and/or magnesium stearate, many of which are well known in the coating art. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially triethyl citrate, tributyl citrate, acteyltriethyl citrate, dibutyl phthalate, diethyl phthalate, polyethylene glycol, acetylated monoglycerides propylene glycol, and triacetin. Conventional coating techniques such as fluid-bed or pan coating are employed to apply the coating. Coating thickness must be sufficient to ensure that the oral dosage form remains essentially intact until the desired site of delivery in the small intestine is reached.

The solid oral dosage form may be in the form of a coated compressed tablet which contains particles or granules of the bisphosphonate active ingredient and the chelating agent, or of a soft or hard capsule (e.g., gelatin, starch, or hydroxypropylmethylcellulose), coated or uncoated, which contains beads or particles of the bisphosphonate active ingredient and the chelating agent, which themselves are enterically coated. In an embodiment of the invention the tablets are compressed and the tablet is enteric coated.

Suitable enteric coating materials include Eudragit L-100®, Eudragit L 30 D-55®, cellulose acetate phthalate, shellac, or any enteric coating material that dissolves at about pH 5.5 to about 6.5. The enteric coating is applied using various spray techniques known to one skilled in the art. The enteric coating may further comprise one or more pharmaceutically-acceptable excipients including, but not limited to, talc, triethyl citrate, polyethylene glycol, Tween 80® (polyoxyethylene sorbitan monooleate, available from Sigma Chemical CO., St. Louis, Mo.), castor oil. The enteric coating is applied to the tablet core to provide a weight gain of 2.5% to 40%.

The tablet core comprises a bisphosphonate active ingredient, a chelating agent, and may contain one or more pharmaceutically-acceptable excipients. Suitable excipients include, but are not limited to, crystalline cellulose, lactose, calcium hydrogen phosphate, polyvinylpyrrolidone, magnesium stearate, sucrose, starch, magnesium oxide, sodium starch glycolate and sodium lauryl sulfate.

Time Dependent Delivery Systems

In another embodiment of the invention, delivery of the risedronate and the chelating agent to the small intestine is achieved through the use of a time dependent delivery system. Given established transit times after gastric emptying, drug and/or chelating agent release can be targeted to the various segments of the small intestine. Approaches to time dependent delivery systems suitable for use in the present invention include, but are not limited to, such devices as the Pulsincap™ (Scherer DDS, Strathclyde, U.K.), the Time Clock™

(Zambon Group, Milan, Italy), and SyncroDose™ (Penwest, Patterson, N.Y.), as well as various coatings which degrade over time to release tablet contents such as hydroxypropylmethylcellulose, hydroxypropylcellulose, or any suitable hydrogel.

In one embodiment of the invention, the time-dependent device Pulsincap™ is used to target delivery of the active ingredient and the chelating agent to the small intestine. The active ingredient and other excipients, including the chelating agent, are contained inside the Pulsincap™ water-insoluble capsule by means of a hydrogel plug which is covered by a water-soluble cap. The entire dose form is optionally coated in an enteric-coating material to protect the dose form from degradation while in transit through the upper GI tract. When the patient swallows the Pulsincap™ dosage form, the water-soluble cap dissolves and exposes the hydrogel plug to gastric and/or intestinal fluids. The hydrogel cap then swells, and eventually pops out of the capsule body, thus releasing the capsule contents. Release of the capsule contents can be targeted to specific regions of the small intestine by modifying the hydrogel plug properties. Watts, Peter J. & Illum, Lisbeth, Drug Dev. and Indus. Pharm., 23(9): 893-917 (1997).

In one embodiment of the invention, a time dependent coating is applied over a compressed tablet and then an enteric coating is applied over the time dependent coating. This is used to target delivery of the active ingredient and the chelating agent to the small intestine. The active ingredient and other excipients, including the chelating agent, are contained inside the core tablet. The entire dose form is coated with a time dependent coating and then an enteric coating. The enteric-coating material is to protect the dose form from degradation while in transit through the upper GI tract. When the patient swallows the dosage form the enteric coating dissolves after the dosage form leaves the stomach and then the core tablet starts to swell. Eventually, at a predetermined time in the small intestine fluids, the time dependent coating will rupture and releases the contents of the core tablet in the small intestine. Release of the core tablet contents can be targeted to specific regions of the small intestine by modifying the core tablet, time dependent coating and/or the enteric coating.

Pharmaceutically-acceptable Excipients

Pharmaceutically-acceptable excipients include, but are not limited to, polymers, resins, plasticizers, fillers, lubricants, diluents, binders, disintegrants, solvents, co-solvents, surfactants, buffer systems, preservatives, sweetener agents, flavoring agents, pharmaceutical-grade dyes or pigments, chelating agents, viscosity agents, and combinations thereof. Pharmaceutically-acceptable excipients can be used in any component in making the oral dosage form, i.e. core tablet or coating.

Flavoring agents and dyes and pigments among those useful herein include but are not limited to those described in Handbook of Pharmaceutical Excipients (4th Ed., Pharmaceutical Press 2003).

Suitable co-solvents include, but are not limited to, ethanol, isopropanol, and acetone.

Suitable surfactants include, but are not limited to, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters, simethicone emulsion, sodium lauryl sulfate, Tween 80®, and lanolin esters and ethers.

Suitable preservatives include, but are not limited to, phenol, alkyl esters of parahydroxybenzoic acid, benzoic acid and the salts thereof, boric acid and the salts thereof, sorbic acid and the salts thereof, chlorbutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben.

Suitable fillers include, but are not limited to, starch, lactose, sucrose, maltodextrin, and microcrystalline cellulose.

Suitable plasticizers include, but are not limited to, triethyl citrate, polyethylene glycol, propylene glycol, dibutyl phthalate, castor oil, acetylated monoglycerides, and triacetin.

Suitable polymers include, but are not limited to, ethylcellulose, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, and Eudragit® L 30-D, Eudragit® L 100-55, (Röhm Pharma GmbH and Co. KG, Darmstadt, Germany), and Acryl-EZE® and Sureteric® (Colorcon, Inc., West Point, Pa.).

Suitable lubricants include, but are not limited to, magnesium stearate, stearic acid, and talc.

Methods of Use

The present invention further relates to a method of treating or preventing diseases characterized by abnormal calcium and phosphate metabolism comprising administering to a human or other mammal in need thereof a safe and effective amount of a pharmaceutical composition delivered to said human or other mammal via the oral dosage forms described herein.

Diseases characterized by abnormal calcium and phosphate metabolism include, but are not limited to, osteoporosis, Paget's disease (osteitis deformans), hyperparathyroidism, hypercalcemia of malignancy, osteolytic bone metastasis, myositis ossificans progressiva, calcinosis universalis, and such afflictions as arthritis, neuritis, bursitis, tendonitis, and other inflammatory conditions which predispose involved tissue to deposition of calcium phosphates.

The oral dosage forms of the present invention are suitable for administration to a patient according to a continuous dosing interval of daily, weekly, three times per month, twice monthly, and monthly.

Kits

The present invention further comprises kits that are particularly useful for administering the oral dosage forms described herein according to a continuous dosing schedule of daily, weekly, three times per month, twice monthly, or monthly. Such kits comprise one or more oral dosage forms comprising risedronate and a chelating agent and a means for facilitating compliance with methods of this invention. Such kits provide a convenient and effective means for assuring that the subject to be treated takes the appropriate oral dosage form in the correct dosage and in the correct manner. The compliance means of such kits includes any means which facilitates administering the active according to a method of this invention. Such compliance means includes instructions, packaging, and dispensing means, and combinations thereof. The kits can also comprise a means for aiding the memory, including but not limited to a listing of the days of the week, numbering, illustrations, arrows, Braille, calendar stickers, reminder cards, or other means specifically selected by the patient. Examples of packaging and dispensing means are well known in the art, including those described in U.S. Pat. No. 4,761,406, Flora et al., issued Aug. 2, 1988; and U.S. Pat. No. 4,812,311, Uchtman, issued Mar. 14, 1989.

Optionally, the kits can comprise at least one oral dosage form comprising a risedronate and a chelating agent and at least one oral dosage form of an accompanying nutrient. Preferred nutrients are calcium and/or vitamin D. Oral forms of calcium suitable for use in the present invention include

capsules, compressed tablets, chewable tablets, and the like. Typical salt forms of calcium suitable for use in the present invention include but are not limited to calcium carbonate, calcium citrate, calcium malate, calcium citrate malate, calcium glubionate, calcium gluceptate, calcium gluconate, calcium lactate, dibasic calcium phosphate, and tribasic calcium phosphate. In one embodiment, kits of the present invention may include tablets comprising 400 mg to 1500 mg calcium.

The term "vitamin D," as used herein, refers to any form of vitamin D that may be administered to a mammal as a nutrient. Vitamin D is metabolized in the body to provide what is often referred to as "activated" forms of vitamin D. The term "vitamin D" can include activated and non-activated forms of vitamin D, as well as precursors and metabolites of such forms. Precursors of these activated forms include vitamin D_2 (ergocalciferol, produced in plants) and vitamin D_3 (cholecalciferol, produced in skin and found in animal sources and used to fortify foods). Vitamins D_2 and D_3 have similar biological efficacy in humans. Non-activated metabolites of vitamins D_2 and D_3 include hydroxylated forms of vitamins D_2 and D_3. Activated vitamin D analogs cannot be administered in large doses on an intermittent schedule, due to their toxicity in mammals. However, non-activated vitamin D_2, vitamin D_3, and their metabolites may be administered in larger doses than "active" forms of vitamin D on an intermittent basis, without toxicity. In one embodiment, kits of the present invention may include tablets comprising 100 IU to 10,000 IU of vitamin D.

In another embodiment, kits of the present invention may include one or more nutrient tablets comprising both calcium and vitamin D. In a further embodiment, the unit dose of nutrient comprises about 600 mg calcium and about 400 IU vitamin D.

The following non-limiting examples illustrate the formulations, processes, and uses of the present invention.

EXAMPLES

Example I

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	143.3 mg
Triethylcitrate	6.45 mg
Talc	21.5 mg
Red Iron Oxide	0.22 mg
Simethicone emulsion (30%)	0.43 mg
Polysorbate 80	0.43 mg
Purified Water	307.7 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to the pigment suspension and mixed for at least 45 minutes. The Eudragit L 30 D-55 solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated, using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 30% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 35 mg risedronate tablets, each tablet weighing 240 mg and each containing:

Active Ingredients:	
Risedronate Sodium	35 mg*
Chelant:	
Disodium EDTA	100 mg
Excipients	
Microcrystalline cellulose	85.8 mg
Sodium starch glycolate	6 mg
Stearic acid	12 mg
Magnesium stearate	1.2 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, edetate disodium, sodium starch glycolate, and microcrystalline cellulose are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately ten minutes with the intensifier bar on. The stearic acid and magnesium stearate are screened and added to the blender. The blend is mixed for approximately 3 minutes with the intensifier bar off. The blend is compressed into tablets using a suitable tablet press.

Example II

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate sodium are prepared as described below, using a similar method set forth in Example I.

A coating composition is prepared from a lacquer containing the following excipients, per tablet:

Ingredients:	
Acryl-EZE (manufactured by Colorcon, Inc., West Point, Pa.) dry solids	200 mg
Purified Water	950 mg

A coating weight of 40% weight gain is applied by conventional pan coating to tablets containing 150 mg risedr-

onate and 75 mg EDTA so that oval tablets, each weighing 500 mg, result. The composition of each tablet is as follows:

Active Ingredients:	
Risedronate Sodium	150 mg*
Chelant:	
Disodium EDTA	75 mg
Excipients	
Mannitol	100 mg
Starch 1500	159 mg
Silicon Dioxide	1 mg
Stearic acid	15 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Example III

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	51.37 mg
Triethylcitrate	1.54 mg
Talc	11.56 mg
Red Iron Oxide	0.02 mg
Simethicone emulsion (30%)	0.05 mg
Polysorbate 80	0.15 mg
Purified Water	79.21 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to the pigment suspension and mixed for at least 45 minutes. The Eudragit L 30 D-55 solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated, using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of approximately 10% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 35 mg risedronate tablets, each tablet weighing 290 mg and each containing:

Active Ingredients:	
Risedronate Sodium	35 mg*
Chelant:	
Disodium EDTA	100 mg
Excipients:	
ProSolv SMCC 90	131.8 mg
Stearic Acid	14.5 mg
Sodium Starch Glycolate	7.25
Magnesium stearate	1.5 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, edetate disodium, sodium starch glycolate, ½ of the ProSolv SMCC90, ½ of the stearic acid and ½ of the magnesium stearate are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately twenty minutes with the intensifier bar on and then chilsonated and milled. The remaining ProSolv SMCC90, and stearic acid are added and mixed for another 10 minutes. The remaining magnesium stearate is screened and added to the blender with the granulation. The blend is mixed for approximately 3 minutes with the intensifier bar off. The blend is compressed into tablets using a suitable tablet press.

Example IV

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	66.10 mg
Triethylcitrate	1.99 mg
Talc	14.87 mg
Yellow Iron Oxide	0.02 mg
White Chromatone	0.07
Simethicone emulsion (30%)	0.06 mg
Polysorbate 80	0.20 mg
Purified Water	101.89 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, White Chromatone, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to

the pigment suspension and mixed for at least 45 minutes. The Eudragit L 30 D-55 solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated, using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of approximately 9% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 50 mg risedronate tablets, each tablet weighing 414.3 mg and each containing:

Active Ingredients:	
Risedronate Sodium	50 mg*
Chelant:	
Disodium EDTA	142.9 mg
Excipients:	
ProSolv SMCC 90	188.3 mg
Stearic Acid	20.7 mg
Sodium Starch Glycolate	10.4
Magnesium stearate	2.0 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, edetate disodium, sodium starch glycolate, ½ of the ProSolv SMCC90, ½ of the stearic acid and ½ of the magnesium stearate are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately twenty minutes with the intensifier bar on and then chilsonated and milled. The remaining ProSolv SMCC90, and stearic acid are added and mixed for another 10 minutes. The remaining magnesium stearate is screened and added to the blender with the granulation. The blend is mixed for approximately 3 minutes with the intensifier bar off. The blend is compressed into tablets using a suitable tablet press.

Example V

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	150 mg
Triethylcitrate	10 mg
Talc	30 mg
Black Iron Oxide	0.1 mg
Purified Water	250 mg

The enteric coating is prepared using the following method:

The talc and black iron oxide are added to a portion of purified water and mixed until uniform. The triethylcitrate is added with continuous mixing. The resulting pigment suspension is next passed through a screen or a suitable mill to break up agglomerates. The Eudragit L 30 D-55® is screened and then added to a suitable vessel and diluted with a portion of the purified water. The pigment suspension is then added to the diluted Eudragit suspension and mixed until uniform.

In a suitable coating pan, the compressed tablets (10 kg) containing risedronate and EDTA, described below, are warmed to about 30-35° C. The enteric coating suspension is sprayed onto the tablets at approximately 30 grams per minute. When the spray cycle is completed, the temperature is reduced and the tablets are removed and dried at 30-35° C. for approximately 1 hour.

A coating weight gain of 35% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 5 mg risedronate tablets, each tablet weighing 240 mg and each containing:

Active Ingredients:	
Risedronate sodium	5.0 mg*
Chelant:	
Disodium EDTA	75.0 mg
Excipients	
Microcrystalline cellulose	149.5 mg
Sodium starch glycolate	9 mg
Stearic acid	1.5 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The tablets are prepared by sieving the risedronate active ingredient and the EDTA with ½ of the microcrystalline cellulose into a twin shell blender. The blend is then mixed until uniform. Then, ½ of the stearic acid is added and the blend is mixed further. The blend is then is roller compacted and milled. The remaining microcrystalline cellulose and sodium starch glycolate are added and mixed until uniform.

The remaining stearic acid is then added and mixed until adequate lubrication is achieved. Tablets are then compressed on a rotary tablet press.

Example VI

Time Dependent and Enteric Coated Tablets Containing Risedronate and Sodium Citrate

Time Dependent and Enteric Tablets containing risedronate and sodium citrate are made by preparing a two layer coating composition and compressed tablets containing risedronate and sodium citrate and then applying said coating composition to said tablets.

The first layer (Time Dependent Coating Layer) coating composition is prepared in the form of a polymer containing the following excipients, per tablet:

A. Acid Soluble Coating Layer

Ingredients:	
Ethylcellulose	40.0 mg
Dibuty Sebacate	8 mg
Toluene	250 mg
Ethyl Alcohole	70 mg

The acid soluble coating is prepared using the following method:

A solution is prepared by adding the ethylcellulose to approximately two-thirds of the toluene:ethyl alcohol mixture while mixing. The solution is mixed for at least two hours. The dibuty sebacate is added and mixed for an additional two hours. The resulting coating solution is screened and mixed throughout the coating process.

B. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbHand Co. KG, Darmstadt, Germany)	150 mg
Triethyl citrate	6.0 mg
Talc	15.0 mg
Red Iron Oxide	0.25 mg
Purified Water	260 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The Eudragit L 30 D-55 solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process.

The compressed tablets are transferred to the coating pan and preheated with occasional jogging. The compressed tablets are coated with the Time Dependent Coating then with the Enteric Coating Suspension using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 10% for the Time Dependent Coating and 13% Enteric Coating (total solids compared to that of the core tablet weight) is applied by spraying the above composition (A and B) onto compressed tablets containing risedronate and sodium citrate prepared in Part C below.

C. Compressed Tablets Containing Risedronate and Sodium Citrate

The Acid Soluble Coating and the Enteric Coating suspension prepared in Part A and B above is sprayed onto 5 mg risedronate tablets, each tablet weighing 500 mg and each containing:

Active Ingredients:	
Risedronate Sodium	5 mg*
Chelant:	
Sodium Citrate	250 mg
Excipient	
Microcrystalline Cellulose	109.5 mg
Croscarmellose Sodium	25.0 mg
Mannitol	100 mg
Magnesium stearate	0.5 mg
Polyvinylpyrrolidone	10 mg
Purified Water	100.0 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, sodium citrate, microcrystalline cellulose, croscarmellose sodium, mannitol and polyvinylpyrrolidone are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately ten minutes with the intensifier bar on and granulated with purified water for 15 minutes. The mixture is dried overnight at 30° C., passed through a mill. The magnesium stearate is screened and added to the blender. The blend is mixed for approximately 3 minutes with the intensifier bar off. The blend is compressed into tablets using a suitable tablet press.

Example VII

Time Dependent Delivery Tablets Containing Risedronate and EDTA

Time dependent delivery tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

A coating composition is prepared containing the following excipients, per tablet:

A. Coating Suspension

Excipients:	
Carnauba Wax	80 mg
Beeswax	35 mg
Polyoxyethylene sorbitan monooleate	11 mg
Hydroxypropylmethylcellulose	24 mg
Purified Water	500 mL

The coating is prepared using the following method:

The carnauba wax, beeswax, polyoxyethlyene sorbitan monooleate, and hydroxypropylmethylcellulose are added to the purified water at 60° C. and mixed for 3 hours. The resulting coating mixture is screened and mixed throughout

the coating process. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated, using a typical pan coating process until the required quantity of coating solution (at 60° C.) has been applied. Tablets are then cooled and collected in suitable containers.

A coating weight gain of 30% (total solids) is applied by spraying the above composition onto compressed tablets containing risedronate and EDTA, prepared in Part B below.

B. Compressed Tablets Containing Risedronate and EDTA

The coating suspension prepared in Part A above is sprayed onto 35 mg risedronate tablets, each tablet weighing 500 mg and each containing:

Active Ingredients:	
Risedronate Sodium	35 mg*
Chelant:	
Disodium EDTA	150 mg
Excipients:	
Microcrystalline cellulose	50 mg
Spray Dried Lactose	245 mg
Sodium starch glycolate	15 mg
Magnesium stearate	5 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Tablets having the composition set forth above are prepared as follows:

The risedronate sodium, EDTA disodium, microcrystalline cellulose, Spray dried lactose and sodium starch glycolate are passed through a mill and added to a blender equipped with an intensifier bar. The mixture is blended for approximately ten minutes with the intensifier bar on. The magnesium stearate is screened and added to the blender. The blend is mixed for approximately 3 minutes with the intensifier bar off. The blend is compressed into tablets using a suitable tablet press.

Example VIII

Enteric-Coated Tablets Containing Risedronate and EDTA

Enteric-coated tablets containing risedronate and EDTA are made by preparing a coating composition and compressed tablets containing risedronate and EDTA, and then applying said coating composition to said tablets.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Ingredients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbH and Co. KG, Darmstadt, Germany)	47.8 mg
Triethylcitrate	2.15 mg
Talc	7.17 mg
Red Iron Oxide	0.07 mg
Simethicone emulsion (30%)	0.14 mg
Polysorbate 80	0.14 mg
Purified Water	102.6 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to the pigment suspension and mixed for at least 45 minutes. The Eudragit L30 D-55® solution and triethyl citrate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process. The core tablets are transferred to the coating pan and preheated with occasional jogging. Tablets are coated, using a typical pan coating process until the required quantity of coating solution has been applied. Tablets are then cooled and collected in suitable containers.

The enteric coating suspension prepared in Part A above is sprayed onto 35 mg risedronate tablets, each tablet weighing 240 mg and prepared as in Example IB

Example IX

Enteric-Coated Soft Gelatin Capsules Containing Risedronate and Disodium EDTA

Enteric-coated capsules containing risedronate and EDTA are made by preparing a coating composition and soft gelatin capsules containing risedronate and EDTA, and then applying said coating composition to said soft gelatin capsules.

An enteric coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

A. Enteric Coating Suspension

Excipients:	
Eudragit L 30 D-55 ® (wet basis) (manufactured by Röhm Pharma GmbHand Co. KG, Darmstadt, Germany)	200.0 mg
Dibutyl phthalate	10.0 mg
Talc	30.0 mg
Red Iron Oxide	0.25 mg
Simethicone emulsion (30%)	0.50 mg
Polysorbate 80	0.50 mg
Purified Water	350 mg

The enteric coating is prepared using the following method:

A pigment suspension is prepared by adding polysorbate 80, ground ferric oxide, and talc to approximately two-thirds of the purified water while mixing. The suspension is mixed for at least two hours. The 30% simethicone emulsion and the remaining water are added to the pigment suspension and mixed for at least 45 minutes. The Eudragit L 30 D-55 solution and dibutylphthalate are combined and mixed for at least 45 minutes. The pigment suspension is then added to the Eudragit solution and mixed for 30 to 60 minutes. The resulting coating suspension is screened and mixed throughout the coating process. The soft gelatin capsules are transferred to the coating pan and preheated with occasional jogging. The soft gelatin capsules are coated, using a typical pan coating process until the required quantity of coating solution has been applied. Capsules are then cooled and collected in suitable containers.

A coating weight gain of 13% (total solids) is applied by spraying the above composition onto soft gelatin capsules containing risedronate and EDTA, prepared in Part B below.

B. Soft Gelating Capsules Containing Risedronate and EDTA

The enteric coating suspension prepared in Part A above is sprayed onto 50 mg risedronate soft gelatin capsules, each weighing 764 mg and each containing:

Fill Composition	
Risedronate sodium	50 mg*
Oleoyl Macrogol-6 Glycerides	370 mg
Colloidal Silicon Dioxide	5 mg
Disodium EDTA	125 mg
Total	550 mg
Gel Shell Composition	
Gelatin	123.4 mg
Glycerin	44.1 mg
Anhydrized Liquid Sorbitol (Sorbitol Special, 76%)	27.1 mg
Purified Water	17.1 mg
Titanium dioxide	1.0 mg
FD&C Red No. 40, E129	0.96 mg
FD&C Blue No. 1, E133	0.30 mg
Total	214 mg
Total Capsule weight	764 mg

*This amount is calculated on a risedronate anhydrous monosodium salt basis.

Soft gelatin capsules having the composition set forth above are prepared as follows:

The Oleoyl Macrogol-6 Glycerides is added to a suspension tank equipped with an overhead mixer. The risedronate sodium, disodium EDTA, colloidal silicon dioxide are passed through a mill and added to the Oleoyl Macrogol-6 Glycerides with continued mixing. The mixture is blended for approximately 60 minutes. The blend is then deaerated and ready for filling into capsules. With mixing, the glycerin, sorbitol special, and purified water are combined in a heated vacuum vessel. Heat is applied until the temperature reaches at least 80° C., then the gelatin is added and mixed for 75 minutes. The gel mass is examined for complete dissolution of particles. If needed, continued heating and mixing is applied until there is no visual evidence of undissolved particles. The gel mass is deaerated, then the titanium dioxide, FD&C Red No. 40 and FD&C Blue No. 1 are added with continued mixing. The gel mass is discharged into heated gel holding tanks for subsequent processing. The fill material is then encapsulated on a soft gelatin capsule filler.

Example X

A 65 kg woman diagnosed with postmenopausal osteoporosis is prescribed the enteric-coated oral dosage form of Example I, to be taken once weekly, comprising 35 mg risedronate and 100 mg Disodium EDTA. The patient takes the oral dosage form with breakfast once per week. The amount of risedronate absorbed is equivalent to that of a 35 mg immediate released tablet taken in a fasted state.

Example XI

A 70 kg man diagnosed with prostate cancer and high bone turnover is prescribed the enteric-coated oral dosage form of Example I, to be taken once weekly, comprising 35 mg risedronate and 150 mg citric acid. The patient takes the oral dosage form once per week, immediately before going to sleep. The patient does not experience upper GI irritation or discomfort.

Example XII

A group of women diagnosed with postmenopausal osteoporosis are prescribed the enteric-coated oral dosage form of Example IV comprising 50 mg risedronate, to be taken once weekly. The patients take the oral dosage form with breakfast once per week. The amount of risedronate absorbed is equivalent to that of a 35 mg immediate released tablet taken per label, at 30 minutes before food or drink.

All documents cited are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

What is claimed is:

1. An oral dosage form having pharmaceutically effective absorption comprising:
   (a) from about about 1 mg to about 250 mg of a bisphosphonate selected from the group consisting of risedronate and acids, salts, and esters thereof;
   (b) from about 10 mg to about 500 mg of EDTA; and
   (c) a delayed release mechanism to immediately release the risedronate and the EDTA in the small intestine; wherein said composition weighs no greater than 1 gram.

2. The oral dosage form of claim 1 wherein the EDTA is disodium EDTA.

3. The oral dosage form of claim 1 wherein the delayed release mechanism is selected from the group consisting of pH triggered delivery systems, time dependent delivery systems and mixtures thereof.

4. The oral dosage form of claim 3 wherein the delayed release mechanism is a pH triggered delivery system.

5. The oral dosage form of claim 4 wherein the pH triggered delivery system comprises an enteric coating.

6. The oral dosage form of claim 5 wherein the enteric coating disintegrates between about pH 5.5 and about pH 6.5.

7. The oral dosage of claim 5 which comprises from about 75 mg to about 250 mg of EDTA, wherein the EDTA is disodium EDTA.

8. An oral dosage form having pharmaceutically effective absorption comprising:
   (a) from about 1 mg to about 250 mg risedronate sodium;
   (b) from about 25 mg to about 500 mg of disodium EDTA; and
   (c) an enteric coating which provides for immediate release of the risedronate sodium and the disodium EDTA in the small intestine of a mammal.

9. The oral dosage form of claim 8 comprising from about 35 mg to about 50 mg of the risedronate sodium.

10. A method for treating a disease selected from the group consisting of osteoporosis, Paget's disease, hyperparathyroidism, hypercalcemia of malignancy, osteolytic bone metastasis, and combinations thereof, comprising administering to a human or other mammal in need thereof a safe and effective amount of the oral dosage form of claim 1.

11. The method of claim 10 wherein the disease is osteoporosis.

12. The method of claim 11 wherein the oral dosage form is administered according to a continuous schedule having a

dosing interval selected from the group consisting of daily, weekly, three times per month, twice monthly, and once monthly.

13. The method of claim **12** wherein the oral dosage form is administered weekly.

14. The method of claim **10** wherein the oral dosage form is administered with or without food.

15. The oral dosage form of claim **8** comprising from about 15 mg to about 55 mg of the risedronate sodium.

16. The oral dosage form of claim **15** comprising from about 75 mg to about 250 mg of the disodium EDTA.

17. The oral dosage form of claim **16** comprising about 35 mg of the risedronate sodium.

18. The oral dosage form of claim **17** wherein the enteric coating is a methacrylic acid copolymer.

19. The oral dosage form of claim **17** comprising about 100 mg of the disodium EDTA.

20. The oral dosage form of claim **19** wherein the enteric coating is a methacrylic acid copolymer.

21. The oral dosage form of claim **8** comprising from about 50 mg to about 280 mg of the risedronate sodium.

22. The oral dosage form of claim **21** comprising from about 75 mg to about 250 mg of the disodium EDTA.

23. The oral dosage form of claim **22** comprising about 150 mg of the risedronate sodium.

24. The oral dosage form of claim **23** wherein the enteric coating is a methacrylic acid copolymer.

25. The oral dosage form of claim **23** comprising about 100 mg of the disodium EDTA.

26. The oral dosage form of claim **25** wherein the enteric coating is a methacrylic acid copolymer.

27. A method for treating osteoporosis comprising administering to a human or other mammal in need thereof a safe and effective amount of the oral dosage form of claim **17**.

28. The method of claim **27** wherein the oral dosage form is administered with or without food.

29. A method for treating osteoporosis comprising administering to a human or other mammal in need thereof a safe and effective amount of the oral dosage form of claim **25**.

30. The method of claim **29** wherein the oral dosage form is administered with or without food.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,645,460 B2
APPLICATION NO. : 11/286875
DATED : January 12, 2010
INVENTOR(S) : Dansereau et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 999 days.

Signed and Sealed this

Twenty-eighth Day of December, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,645,460 B2
APPLICATION NO. : 11/286875
DATED : January 12, 2010
INVENTOR(S) : Richard John Dansereau et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 999 days.

ON THE TITLE PAGE [56] REFERENCES CITED:

Other Publications, "Deliver" should read --Delivery--.

COLUMN 2:

Line 52, "it was" should read --it is--.

COLUMN 3:

Line 6, "instruct" should read --instructs--;
Line 8, "are" should be deleted; and
Line 9, "instructed" should read --instructs them--.

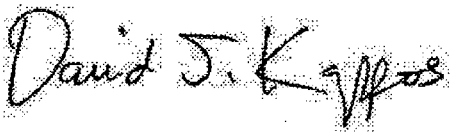
COLUMN 4:

Line 18, "is" should read --being--; and
Line 27, "active" should read --active ingredient--.

COLUMN 5:

Line 14, "active" should read --active ingredient--.

Signed and Sealed this
Eighteenth Day of January, 2011



David J. Kappos
Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)
U.S. Pat. No. 7,645,460 B2

COLUMN 8:

Line 59, "active" should read --active ingredient--.

COLUMN 9:

Line 21, "the.ileum" should read --the ileum.--.

COLUMN 10:

Line 23, "acteyltriethyl" should read --acetyltriethyl--; and
Line 48, "CO.," should read --Co.,--.

COLUMN 12:

Line 52, "active" should read --active ingredient--.

COLUMN 14:

Line 4, "Eudragit L30 D-55" should read --Eudragit L30 D-55®--; and
Line 7, "Eudragit" should read --Eudragit®--.

COLUMN 15:

Line 53, "Eudragit L30 D-55" should read --Eudragit L30 D-55®--; and
Line 56, "Eudragit" should read --Eudragit®--.

COLUMN 17:

Line 2, "Eudragit L30 D-55" should read --Eudragit L30 D-55®--; and
Line 4, "Eudragit" should read --Eudragit®--.

COLUMN 18:

Line 26, "Eudragit" should read --Eudragit®--.

COLUMN 19:

Line 24, "Dibuty Sebacate" should read --Dibutyl Sebacate--;
Line 26, "Alcoholc" should read --Alcohol--;
Line 34, "dibuty sebacate" should read --dibutyl sebacate--;
Line 42, "Röhm Pharma GmbHand Co." should read --Röhm Pharma GmbH and Co.--;
Line 52, "oxide," should read --oxide--;
Line 53, "Eudragit L30 D-55" should read --Eudragit L30 D-55®--;
Line 55, "Eudragit" should read --Eudragit®--; and

CERTIFICATE OF CORRECTION (continued)
U.S. Pat. No. 7,645,460 B2

Line 67, "13% Enteric" should read --13% for the Enteric--.

COLUMN 21:

Line 33, "Spray" should read --spray--.

COLUMN 22:

Line 10, "Eudragit" should read --Eudragit®--;
Line 38, "Röhm Pharma GmbHand Co. KG," should read --Röhm Pharma GmbH and Co. KG,--;
Line 54, "Eudragit L30 D-55" should read --Eudragit L30 D-55®--; and
Line 57, "Eudragit" should read --Eudragit®--.

COLUMN 24:

Line 25, "about about" should read --about--.

CERTIFICATE OF SERVICE

I hereby certify that on June 26, 2015, a true and correct copy of the foregoing was electronically filed with the Clerk of Court using the CM/ECF System, and thereby served upon the following counsel:

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/s/ Jeffrey B. Elikan
Jeffrey B. Elikan

Dated: June 26, 2015

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B)(i) because this brief contains 13,979 words, excluding the parts of the brief exempted by Fed. R. App. 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word using 14-point Times New Roman font.

/s/ Jeffrey B. Elikan
Jeffrey B. Elikan

Dated: June 26, 2015